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THE MONTH

ADVANCES in treatment, the subject of our October issue every year, can never be restricted to any precise chronological period. Indeed, to attempt to do so would be to destroy the whole aim of this annual special number. The vociferously acclaimed 'wonder drug' of today is so often the forgotten drug of tomorrow. As the corticosteroids, tranquillizers, antibiotics and hypotensive agents pour forth from the pharmaceutical mill, caution is increasingly called for on the part of the practitioner. The potency of a new drug, hailed as a virtue by the manufacturer and the academic pharmacologist, may be anything but an asset when the drug is used in the rough and tumble of general practice. 'Life is very sweet, brother', and the practitioner whose patient happens to be one of those who make up the 'very rare' fatality or near-fatality of the investigator's report, cannot but wonder whether in the future he will not adhere to the old and proven. Risks, of course, must be taken on occasion, and the main function of our annual 'Advances in Treatment' number is to provide our readers with the considered views of the experts on the practical value of the current trends in therapy. That this meets a very real need is suggested by the fact that during recent years requests to republish it have been received from Scandinavia, The Balkans, Turkey and South America.

The Symposium

So many wild and woolly statements are bandied about these days by the politicians concerning the sins of omission (and commission) of pharmaceutical manufacturers, pharmacists, and doctors, that it is refreshing to come across some more or less precise statistics on the subject. These are contained in Part I of the Report of the Ministry of Health for 1957, and take the form of an analysis of 72,596 prescriptions dispensed by a representative sample of pharmacists during 1957. The various drugs are divided into therapeutic categories, and a comparison is made of the percentage of total numbers of prescriptions and the percentage of total ingredient costs for each category.

Prescribing Habits

Antibiotics were the most expensive item, being responsible for 19.94 per cent. of the total ingredient cost, but they were responsible for only 7.19 per cent. of the total number of prescriptions. The most frequently prescribed drugs were cough preparations, which constituted 11.28 per cent.

of the total number of prescriptions but were responsible for only 5.1 per cent. of the total ingredient cost. After antibiotics, hormones (other than sex hormones, but including corticosteroids) were the most expensive item, being responsible for 9.72 per cent. of the cost but only 5.11 per cent. of the number of prescriptions. In spite of all the evidence for the continuing value of sulphonamides, it is of interest to note that they accounted for only 2.38 per cent. of the cost and 3.11 per cent. of the number of prescriptions. There is also some evidence that tonics are on their way out—they represented merely 3.68 per cent. of the total number of prescriptions and 2.53 per cent. of the cost. Barbiturates were prescribed more than twice as often as other sedatives and hypnotics—7.1 per cent. compared with 3.17 per cent. of the prescription—but they were both far exceeded by analgesics and antipyretics which accounted for 10.16 per cent. of the total prescriptions, but only 5.68 per cent. of the total ingredient cost. On the vexed question of proprietary *v* non-proprietary preparations this analysis shows the number of prescriptions to be almost equally divided between the two categories from the point of view of numbers, but the proprietary preparations were responsible for approximately three-quarters of the cost.

Mr. Bevan and the Drug Bill

Mr. Aneurin Bevan, like another famous Welsh politician of an older generation, has all the unpredictability of the Celt. As the Minister of Health who brought the National Health Service into being he has always claimed to be able to speak with authority on the subject. It is meet therefore that his views on the nation's drug bill, as recorded in an article which he contributed to the supplement, 'Scotland's Contribution to Medicine', which *The Scotsman* published to commemorate the first ten years of the National Health Service, should be brought to the attention of as many members of the medical profession as possible. The following excerpt from this article speaks for itself and will not be forgotten, we trust, when the political party to which he belongs comes to power again.

'It was feared by many that a comprehensive health service, freely available at the time of need, would be so open to abuse that it would be bound to break down. These fears have proved to be unjustified . . . There is one slight exception to this; the pharmaceutical side, that is, the cost of drugs and medicines. But even here the situation is not nearly as bad as is made out. In the first instance, a great deal of the increase in the drug bill is explained by the general increase in the cost of living. In the second place many new and beneficial drugs have come on to the market, expensive it is true, but they shorten illness and free beds in hospitals more quickly than before. In the third place, it must be realized that the price the nation pays for drugs covers the cost of the research and experimental work carried out

by the pharmaceutical firms. If they did not do this essential job, it would have to be undertaken by public expenditure'.

Patients and their Drugs

THERE are occasions when the traditional omniscience attributed to him by his patients can be a source of embarrassment to the doctor. No more so than when the patient produces a box of tablets and expects the doctor to recognize their nature from their colour and/or size. At one time this Holmesian quandary was not too difficult of solution. A brown tablet of a certain size with a chocolate flavour was probably glyceryl trinitrate, a dark green one of about the same size was probably digitalis leaf, and a white one was probably phenobarbitone. Today, with the gradual disappearance of mixtures, and their replacement by a multiplicity of physically indeterminate tablets, the problem is almost insoluble.

One aspect of this problem to which a hospital medical officer has just drawn our attention is that 'very often patients come into hospital with boxes of tablets which they say their G.P.s have been giving them for a long time, the name of which is unknown to them. This means that the house physician (or surgeon) has to find out from the G.P. the name of the drug, and this is time-consuming and may also result in delay in treating the patient'. The difficulty is particularly marked when a patient with, say, chronic heart disease or epilepsy, is admitted for an emergency operation such as appendicectomy. Our correspondent appeals to general practitioners, when they send patients to hospital, to make sure that they bring with them a note giving full details of whatever drugs they may be receiving at the time. Undoubtedly many practitioners do provide this information, but there would appear to be quite a considerable minority who omit to do so. We feel certain that it is only necessary to draw their attention to their 'sin of omission' to ensure that in future they will provide this service to their hospital colleagues—and their patients.

An Unethical Practice

As yet another holiday season comes to an end complaints are reappearing of an undesirable practice which would appear to be on the increase. This is for practitioners on holiday to undertake the treatment of their fellow holidaymakers. Two particularly glaring examples have been brought to our attention by a reader in Scotland. One was that of a visiting doctor who telephoned him to say that he was looking after two or three cases of dysentery and could he be told to which laboratory he should send specimens of the stools. The other was the case of a boy who fell on some rocks and, as our correspondent graphically expresses it, 'was passed off as a cracked rib' by a medical visitor. Within twenty-four hours the local general practitioner had to be called in

and the unfortunate boy transferred as quickly as possible to the nearest—but quite distant—hospital where his ruptured liver was dealt with.

What exaggerates the offence—for offence it is—in this particular instance is that the local practitioner in question is dependent upon 'temporary residents' for a not inconsiderable part of his income. Such practices cannot be too strongly condemned. Not only may a life be at stake—as in the second case reported to us—but the whole basis of ethical practice is undermined. No-one objects to a doctor on holiday giving first aid or homely advice to his fellow-visitors, though the wise practitioner knows that the former is much better given by a trained first-aider, and that it is much wiser to leave homely advice to the lay residents of the hotel. What is indefensible is acting as a fellow-visitor's doctor when there is a general practitioner resident in the area. As Dr. David Brown pointed out in his article in our symposium on 'Medical Etiquette' (*The Practitioner*, 1957, **179**, 11), 'there is no branch of the profession in which the need for the exercise of one code of etiquette and ethics is more important than general practice'. Behaviour such as our correspondent describes is the antithesis of good general practice and cannot be too strongly condemned.

An Anatomical Centenary

'GRAY'S Anatomy' has probably been responsible for the burning of more midnight oil than any other textbook in the whole field of medical publications. Undergraduates and postgraduates alike have pored over its pages in an attempt to master the anatomy of the human body, whilst their teachers have always held it in reserve for consultation whenever they wanted to refresh their memory on a forgotten or debatable point. It is therefore with legitimate pride that the publishers have announced the publication of the centenary edition ('Gray's Anatomy'. Thirty-second edition. Edited by T. B. Johnston, C.B.E., M.D., D. V. Davies, M.B., B.S., F. Davies, M.D., D.Sc., F.R.C.S. London: Longmans, Green and Co., 1958. Price £6 6*s*.).

For many years it was a product of St. George's Hospital. The first edition was prepared by Henry Gray, one of the most brilliant young surgeons of his day, who was elected a Fellow of the Royal Society at the age of 25, but died at the age of 34, soon after the publication of the second edition. St. George's men were responsible for successive editions until 1909, when Professor R. Dowden, of Durham, took over, followed in 1930 by Professor T. B. Johnston, of Guy's Hospital. Throughout the years it has maintained its essential attributes of a sound, comprehensive guide to the subject, with increasing emphasis on the functional, as opposed to the structural, aspects of anatomy. As it enters upon its second century it carries with it the good wishes of all those who have benefited from its study in the past, and there is no reason why it should not continue to be the anatomist's bible for many generations to come.

ADVANCES IN MEDICINE

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ADVANCES in treatment take place so continuously, yet so insidiously, that it is a difficult task to review those that may at any time be called recent. It is possible to see two main, but interrelated, lines of development. On the one hand, the more general appreciation of physiological principles has yielded a rich harvest which is well illustrated by our growing understanding of electrolyte metabolism and how to correct its disturbances. On the other, but linked with this more fundamental progress, there has been a formidable multiplication of powerful pharmaceutical agents, so that the practitioner today has at his command therapeutic weapons of a potency which would have astounded his father. From among the multitude of these drugs, certain dramatic landmarks stand out—the antibiotics and the steroid hormones provide obvious examples—but in most instances, the process is one of gradual improvement on existing agents and the advances are only appreciated when there is a pause to take stock.

THE COMPLEXITY OF MEDICAL TREATMENT

If a layman is asked what he understands by treatment, he will usually reply, that it is the cure of disease. Cure, in defiance of its etymology, has come to mean a complete restitution of the *status quo ante* and in this sense is a notion derived from the infective processes. The patient who recovers from pneumococcal pneumonia or meningococcal meningitis may perhaps justifiably be said to have been cured by penicillin. Less than fifty years ago, the infective processes dominated the practice of medicine; our control of them is now such that they scarcely provide a problem, yet our thinking is still largely shaped by our past experiences in their management. Indeed 'cure' cannot any longer be equated with 'treatment'; our therapeutic concern is now with restoration of function and with relief of symptoms. Every man is mortal; he who is cured of meningitis will eventually die of some other disease. Treatment never does more than defer the final issue; but, more positively, its aim may be said to be the prolongation of happy and useful life. Even if this extension be but a few months, a minor therapeutic victory has been won. The disappearance of infections from the dominant position they held has changed the physician's outlook. First, it has stimulated a long overdue interest in prevention of disease and, secondly, it has altered our attitude towards 'incurable' illness. Nowhere is this last more evident than in the field of cancer; energy, ingenuity and research are now devoted to the prolongation of existence in disseminated carcinoma of the breast, in widespread prostatic carcinoma and in acute leukæmia—conditions which would previously have been stigmatized as hopeless and accorded only the traditional exhibition of morphia.

A development which springs in part from this changed attitude and in part from the wealth of potent drugs now available is the increasing complexity of medical treatment. It is this which has led to the growth of specialization and it presents a difficulty which the general practitioner has yet to face. There are many patients suffering from chronic diseases who are undoubtedly best treated in specialized clinics. It is only here that the concentration of experience which enables the best results to be obtained can be acquired. In many of these diseases, too, control requires repeated tests which can only be carried out in a laboratory. Diabetes mellitus is a case in point, although it is a common disorder of which any general practitioner can obtain experience. Leukæmia provides another illustration: assuming patients with this disease to be shared equally between all general practitioners, each would see one case in ten years; in a special clinic, there may be as many as a hundred cases in one year. To this problem there can be no solution but closer cooperation between general practitioner and specialist department.

These trends in treatment are not recent advances. They are the product of the wider view that the profession takes of its functions and they are not without some disadvantages. Medical care is in danger of becoming impersonal. No greater disaster can befall a patient than to be treated by an inchoate committee of specialists, physiotherapists, occupational therapists and social workers, but the individual is of necessity being replaced by a group. It is one of the duties of the family doctor to maintain the tradition of personal service and by giving the group cohesion and unity to transform it into a team.

This altered climate of therapeutic opinion is as important as any advances in the treatment of individual diseases. In a short article, it is impossible to describe more than a few of these and an attempt has been made to select those which underline the general trends already noted.

THE CORTICOSTEROIDS

The introduction of the steroid hormones, cortisone and cortisol (hydrocortisone), has been one of the most important pharmacological achievements of the past decade. Although no-one will be rash enough to challenge this statement, it is of interest to note that these preparations have never effected a 'cure' in the sense already defined; yet there are no other drugs with such wide therapeutic application. They share, too, with many latter-day agents the ability to cause undesirable and, indeed, serious side-effects, even when administered in therapeutic dosage. The natural hormone is cortisol (hydrocortisone), but both it and cortisone exist, and are freely interconvertible, in the body. Their pharmacological activities fall into two groups: glucocorticoid and mineralocorticoid. Among the first are most of those exploited in treatment, whilst the second includes the tubular resorption of sodium with resulting retention of water and the increased loss of potassium, both effects which are generally undesirable. The pharmaceutical chemists have

shown that minor modifications in the structure of these natural steroids lead to major alterations in their pharmacological activities and the last few years have seen the introduction of several synthetic corticosteroids of great value in treatment.

The first step was the production of prednisolone and prednisone (Herzog *et al.*, 1955), the delta-1 analogues of cortisol and cortisone in which a double bond has been introduced between the first two carbon atoms of the steroid ring. These two drugs have some five times the glucocorticoid activity of their naturally occurring analogues but the same mineralocorticoid potency. They can therefore be prescribed in doses which lead to no significant retention of sodium or loss of potassium, while retaining full glucocorticoid effect. A change of activity in the opposite direction is effected by adding a fluorine atom in the 9-alpha position. The product, known as 9α-fluorohydrocortisone (fludrocortisone) (Freed and Sabo, 1954) has a glucocorticoid activity ten times that of cortisone but a mineralocorticoid effect at least one hundred times greater (Garrod *et al.*, 1955). The addition of a 16-hydroxy group to these fluorinated compounds again increases the glucocorticoid potency at the expense of the mineralocorticoid. An example recently introduced to therapeutics is 16-hydroxy-9-alpha-fluoroprednisolone, or triamcinolone, in which the glucocorticoid activity is somewhat greater than that of prednisolone and the mineralocorticoid effect about the same. Its potency does not exceed that of prednisolone sufficiently to give any clear advantage.

There has been little change in the detailed application of these drugs to treatment. The corticosteroids fulfil their physiological function in the control of Addison's disease. There has been some dissatisfaction in the past with the effect of cortisone because its mineralocorticoid potency has not always been sufficient to maintain a normal level of sodium in the blood. This deficiency can now be remedied by adding fludrocortisone to the dose of cortisone or by using a tablet containing both (Leith and Beck, 1957). The place of corticosteroids in the treatment of rheumatoid arthritis is still a matter for debate. In the collagen diseases—polyarteritis nodosa and disseminated lupus erythematosus—there are no other agents with any therapeutic effect, with the possible exception of chloroquine in the second; there is therefore no alternative to their use. The relation between rheumatoid arthritis and these two diseases has long been recognized but there is an increasing weight of opinion which believes that in some way steroid treatment of the first favours the appearance of complicating polyarteritis or disseminated lupus (Kemper *et al.*, 1957). It has been suggested that this development is particularly likely when steroid treatment of rheumatoid arthritis is interrupted (Slocumb, 1953). It is claimed, moreover, that when occurring in this manner these disorders do not show a therapeutic response to the corticosteroids. If these impressions can be supported there is an additional reason for conservatism in treating rheumatoid arthritis with these drugs.

DIURETICS

Until recent years the mercurials have enjoyed an undisputed pre-eminence among the diuretics, but several competitors have now appeared. The first of these, *acetazolamide* ('diamox') was shown to be a powerful inhibitor of carbonic anhydrase as long ago as 1950 (Miller *et al.*). It has therefore the effect of preventing the reaction which normally conserves sodium and of increasing the excretion of alkaline sodium phosphate in the urine. In practical therapeutics, however, it has proved disappointing and cannot rank with the mercurials. It is given orally in doses of 250 mg. daily.

Another group of diuretic drugs is the amino-uracil series, of which *aminometradine* ('mictine') has been in use for some years (Kattus *et al.*, 1952; Hanley, 1956). It possesses about half the diuretic potency of mersalyl and when given in effective doses it often causes gastro-intestinal symptoms. More recently, another member of this series, amisometradine ('rolicton') has been subjected to clinical trial (Jose and Wood, 1958). Gastro-intestinal symptoms were far less frequent and less severe. A careful comparison showed that amisometradine in total dosage of 2.4 g. had only 40 per cent. of the diuretic activity of 2 ml. of mersalyl. It is given by mouth in a dose of 400 mg. three times daily. The diuresis which follows both these compounds is accompanied by loss of sodium and chloride in roughly equimolar quantities and by a small increase in the excretion of potassium.

A more serious rival to the mercurials is to be found in *chlorothiazide* ('saluric'), a diuretic drug synthesized in 1957 by Novello and Sprague. Its action depends upon an enhanced excretion of chloride with an equimolar loss of sodium and thus resembles that of the mercurials; there may be some inhibition of carbonic anhydrase but this contributes little to the total effect (Matheson and Morgan, 1958; Davies and Evans, 1958). Extensive clinical trials have been made and chlorothiazide has won an established place in therapeutics in a very few months. It has been shown to be an efficient diuretic and to be devoid of toxic effects (Bayliss, 1958). Care is necessary when prolonged dosage at a level of 2 g. daily is prescribed, for potassium depletion may occur. In these circumstances, 2 to 6 g. of potassium chloride daily should be administered. In most patients with heart disease such quantities of chlorothiazide are only needed for a few days and the dose can then be reduced to 1 to 1.5 g. on three or four days in each week. It has proved effective in some cases which have been resistant to the mercurials (Bayliss *et al.*, 1958).

In view of the fact that chlorothiazide will cause a much greater loss of potassium and bicarbonate when the serum levels of sodium and chloride are reduced, Watson and his colleagues (1958) have suggested that preliminary dosage with ammonium chloride might enhance its diuretic effect by repairing hypochloræmia. Chlorothiazide has also proved useful in treating the nephrotic syndrome (Arneil, 1958; Slater and Nabarro, 1958) and it is often effective in the control of ascites in hepatic cirrhosis. In this last connexion, the danger of potassium depletion is considerable and a

potassium supplement should always be given. Continuous treatment of cirrhotic patients with chlorothiazide is probably unwise outside hospital (Read *et al.*, 1958).

HYPOTENSIVE DRUGS

During the past ten years a succession of drugs which lower the arterial pressure has been introduced. Those most widely employed have been the ganglion-blocking agents but almost all of these have had undesirable side-effects on the alimentary tract. Moreover, many have shown vagaries of absorption that have made their use hazardous. Until recently, the most convenient has been *mecamylamine* ('inversine'), absorption of which is rapid, regular and virtually complete (Allenby, 1958). This preparation, however, commonly causes constipation and sometimes difficulty with micturition, and the search for agents in which the desired hypotensive effect is dissociated from the unwelcome gastro-intestinal action continues.

Two members of a new group of ganglion-blocking substances originally described by Adamson *et al.* (1956) have recently been submitted to clinical trial and appear to be of promise. The first of these is pentacynium methylsulphate ('presidal'), which was introduced by Locket in 1956. Further experiences in its use have been reported by McKendrick and Jones (1958). After subcutaneous injection the blood pressure starts to fall in ten minutes and reaches its lowest level in an hour to an hour and a half; it remains at this point for several hours, regaining its former height in six to twenty-four hours. After oral administration the drop begins in twenty to thirty minutes and is maximal in one hour. Treatment is started with 50 mg. three times daily by mouth, and the dose is increased 25 mg. at a time at intervals of two days until the desired effect is obtained. Side-effects are mild and their severity decreases with persistence; they are usually limited to blurring of vision and dry mouth; constipation is less common and seldom more than slight. The addition of reserpine enhances the hypotensive effect. Good control of the blood pressure was obtained in 24 of 30 patients treated with pentacynium methylsulphate. A liability to cause drowsiness has been noted by some observers (Cox and Daly, 1958).

More recently, Locket (1958) has reported on another drug which is chemically related to pentacynium methylsulphate; at present, this is designated '189c56'. After a single oral dose the fall in blood pressure is noted in twenty-five to forty-five minutes, the maximal effect is reached in ninety minutes to eight hours, and normal levels are not regained for ten to forty hours. A single daily dose given before breakfast will usually control the pressure throughout the day. The initial dose was 200 mg. and this was increased by 50 mg. daily until a satisfactory hypotensive effect was achieved. Constipation was never more than trivial; ileus and difficulty with micturition did not occur. These claims have not been confirmed but if subsequent trials bear them out, '189c56' may well prove the most effective hypotensive agent yet devised.

Another recently introduced ganglion-blocking drug is *pempidine* ('pero-

lysen'; 'tenormal'), a tertiary amine freely absorbed from the gastro-intestinal tract and more rapidly eliminated than mecamylamine (Harrington *et al.*, 1958). After a single oral dose the hypotensive effect begins in two to four hours, is maximal after another one to three hours and terminates after six to seven hours. It is administered four times daily starting with a dose of 2.5 mg. and increasing by 2.5 mg. until an effective level is reached. It has proved a useful means of controlling hypertension and its rapid elimination has decreased the incidence of side-effects.

The action of chlorothiazide in potentiating the hypotensive drugs was rapidly appreciated. Indeed, it was brought forcibly to the notice of a number of physicians by alarming and unexpected falls in blood pressure. Harrington and Kincaid-Smith (1958) have shown that it depresses the urinary excretion of mecamylamine probably by raising the pH of the urine, and it is doubtful whether there is a true potentiating effect.

ORAL HYPOGLYCÆMIC AGENTS

Since the introduction of insulin, much effort has been devoted to the search for agents which would control diabetes mellitus when given by mouth. The discovery of the hypoglycæmic action of certain sulphonyl ureas in 1955 seemed to bring this goal appreciably nearer. The first agent to be submitted to clinical trial was carbutamide, which proved to be effective in controlling 'mild' diabetes in some middle-aged or elderly patients, but it often produced toxic effects. According to Kirtley (1957), it played some part in causing the death of 8 of 7,193 diabetics treated. For these reasons, it was soon superseded by another member of the same group, tolbutamide. This proved to be as effective in the control of diabetes as its predecessor, but to lack some of its toxic qualities, although rashes have since been reported in 1 per cent. of patients and an occasional instance of cytopenia has been recorded. There is general agreement that tolbutamide will control about 50 per cent. of 'mild' diabetics who cannot be managed solely by dietetic measures. Patients in whom it is most likely to be successful are those over the age of 40 years with little or no tendency to ketosis, who have been controlled by less than 40 units of insulin a day, and in whom the fasting level of blood sugar does not exceed 300 mg. per 100 ml. (Dunlop, 1957).

Considerable interest has centred around the mode of action of the sulphonylureas. There is good evidence that part of the hypoglyæmic effect is due to diminished mobilization of glucose from the liver (Vaughan, 1957). They appear to need the presence of insulin and there may be some increase in the peripheral utilization of glucose (Lundbaek *et al.*, 1958). More recently, another hypoglycæmic agent structurally related to the sulphonylureas has been investigated (Hall *et al.*, 1958). This is phenethyldiguanide (N-beta-phenethylformamidinyl iminourea; D.B.I.). When given in doses of 50 mg. three times daily it will maintain a normal level of blood sugar in a considerable proportion of diabetics, including a number resistant

to tolbutamide. Unfortunately, in about two-thirds of the patients, abdominal pain, nausea, vomiting and diarrhœa necessitate its withdrawal.

The ultimate value of these oral hypoglycæmic agents cannot yet be assessed. They are useful in controlling hyperglycæmia in the middle-aged patient who will not respond to simple dietary restriction. It remains uncertain whether the preservation of a normal level of sugar in the blood is the essence of diabetic treatment and will prevent the appearance of those vascular and renal sequels which are the main menace of the disease today.

CONCLUSION

These four topics do no more than indicate the trends in medical treatment today. None of the drugs described constitutes a 'cure' for any of the diseases in which it is used: relief of symptoms is the aim in all instances. They illustrate, too, the increasing debt the profession owes to the pharmaceutical chemists. While we are pleased to acknowledge our indebtedness, at times we cannot but be overwhelmed by the torrent of powerful preparations with which we are deluged, for they appear with such rapidity that clinical trials are sometimes inadequate.

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ADVANCES IN SURGERY

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Time was when an article on advances in surgery had to compete only with *The Readers Digest*; now 'Your Life in their Hands' has made the problem more complicated. In a war a true advance is a forward step that has been made and consolidated. Many a tree puts forward shoots and buds which do not stand up to the midday sun. A great deal of the so-called growing edge of surgery is of this type. Much of the experimental work going on in the surgical departments throughout the country has no immediate result in advancing surgery but it certainly allows theories to be put to the test and it is a good training ground for systematic research and for the improvement of technique. This experimental work, till proven, can give little help to the practitioner harassed by the problems of general practice. The following remarks are meant to help and guide such a person.

THE BATTLE OF THE BREAST

As many doctors are still in doubt about what is happening in the case of cancer of the breast it should be pointed out that a battle of two ideologies is still waging. For a time the surgical technique for removal of the breast varied, depending upon whether one lived North or South of the Tweed. If North—'Scots wham McWhirter, and later Bruce, has aften led'—the predominant advice was to remove the breast and its tumour but on no account to disturb the axillary glands or lymphatics because in so doing one opened up fresh tissues, and metastases to distant parts were likely to be carried through the mouths of the open lymphatics. It was thought better to leave the glands untouched and to blast them away with adequate deep x-ray therapy. In other parts of Britain the method employed was to do the most extensive operation possible—from clavicle to umbilicus—stripping the axilla and its structures clean of any suspected tissue and thus leaving less for the deep therapy to deal with. One fact emerges clearly with both methods: that the prognosis depends more upon how early the case is dealt with rather than what form of technique is used. The most recent report on this second method comes from the Mayo Clinic (Clagett, 1958). In a large series of cases, using the same selection as the Edinburgh School, their radical methods have given almost 10 per cent. better results as assessed by five-year survival rates (table I).

Phase II of the Breast War is the problem of what is best to do with the recurrent cases in which surgery is no longer possible. Isolated startling successes—all so far temporary—have resulted from different methods often based on different theories: for instance, full dosage with androgens (e.g. testosterone), full dosage with œstrogens (stilbœstrol), ablation of the ovaries, full dosage with cortisone or prednisone or prednisolone, bilateral removal

of the adrenals, destruction of the pituitary gland. This last procedure can be carried out in many ways, e.g. division of the pituitary stalk, implantation of radioactive material into the pituitary fossa using the trans-sphenoidal approach through the nose, complete surgical removal, surgical removal supplemented by leaving in the pituitary fossa some radioactive material to ensure complete destruction in case any active fragments of the pituitary

Place and type of mastectomy	Total number of cases	Total number traced	Lived 5 years or more (per cent.)
Edinburgh Simple with radiotherapy (1941-1947)	1,609	1,609	48.1
Mayo Clinic Radical (1941-1947)	1,918	1,900	59.3
Mayo Clinic Radical (1948-1950)	788	777	64.2

TABLE I.—Five-year survival rates in carcinoma of the breast.

gland have been left behind. At the moment controlled comparisons of these methods are being carried out in many surgical units with particular interest in the relative value of adrenalectomy as compared with hypophysectomy. As yet, with the best results an added eighteen months seems the best that can be offered to the dying patient but the temporary results are so dramatic in certain cases that they have given courage to the surgeon and hope to the patient and in many cases have made the eighteen months well worth while. Unfortunately in other cases, clinically apparently identical, there has been no result and the disease goes on unchecked. This work has stimulated research into the value of vaginal cytology, blood chemistry, and blood steroid values so that some indication may emerge of which cases are likely to respond and why. As yet, these drastic methods have only been used in the hopeless cases which is not a very fair test for any treatment, but the results so far do not warrant its earlier usage as hypophysectomy still has a not inconsiderable morbidity rate, not to mention its mortality rate considering the advanced state of the disease.

SERUM TEST FOR CANCER

The world is waiting for a blood test for the early diagnosis of cancer. Some recent work by Burrows and Neill (1958) has given hope that this may be on the way. In the serum of patients with cancer they found a polypeptide which is not present in the serum of the normal patient. In a series of 301 patients with recognized cancer they report an accurate diagnosis of 96.7 per cent. In a second series of cases free, so far as one could tell, from the disease, out of 207 cases the degree of accuracy was the same, i.e. 96.7 per cent. This is just a beginning; perhaps it is not too much to hope that in the

near future there will be a serum test for cancer as accurate as the Wassermann reaction is for syphilis.

CANCER OF THE ALIMENTARY CANAL

Any progress here is the result of the improved facilities for better and more drastic surgery and the better opportunities for early diagnosis. Man's fingers and the surgical tools have changed little but the surgical ancillaries have advanced greatly. Endoscopy through the various body orifices has given a better knowledge of the lesions as seen from the lumen of the organ. Peritoneoscopy, pleuroscopy and culdoscopy have given further knowledge of the external surface of the organ and have allowed the operability of the disease to be more accurately assessed. A corrected blood chemistry can bring the patient before, during, and after, the operation into a state not only to withstand the immediate ordeal but also the prolonged strain on the vital organs afterwards. Anæsthesia, whether it be hypotensive, hypothermic or with an extra-corporeal circulation, although not yet perfected, is offering the surgeon possibilities that he did not have some years ago. Personal surgical ritual is less fussy and more realistic and the emphasis has switched to the dangers of the modern operating theatre which, with its electrical machines and complicated wiring systems, is now almost as intricate as the engine room of a submarine. With operations, in many cases prolonged, and with so many assistants and technicians each responsible for his own particular apparatus, it is clear that the problem is a very real one. The vital part played by the adrenal gland, whose sudden failure has accounted for some of the otherwise unexplained deaths in the past, is now better understood and a greater effort is made to supplement and support the adrenal secretion by cortisone and to sustain the fallen blood pressure by noradrenaline, so that the pressure never falls sufficiently low to deprive vital organs, such as the kidneys, of their necessary circulation. Blood is perhaps more freely given and possibly antibiotics less commonly used than before and, when used, they are now given in a specific manner and not as a blunderbuss type of umbrella so popular when the antibiotics first appeared.

ULCERATIVE COLITIS

The operative results are so gratifying and the surgical-instrument makers have been so helpful that a promise of comfort and a normal life can be offered to the ileostomy patient. The next few years will prove whether the present rush to retain the rectum—whether healthy or diseased—by reimplanting the ileum into it will stand up to the strain and stress of everyday life. The follow-up after five years will be the acid test. To see the patient put on 56 lb. (25 kg.) in weight in four months and get back to a normal 126 lb. (57 kg.) and able to do everything makes ileostomy one of the most gratifying operations in surgery. When to do it and how long to wait are matters of personal judgment but probably most surgeons can look back on at least one young life that would have been spared if they had operated sooner. A bag, almost invisible under the clothes (one of London's leading

mannequins has one), which can be emptied by the turn of a stopcock; the fitting of a larger bag at night so that sleep is undisturbed; the changing of the adhesive portion from the skin once a week; the ability to enjoy the pleasures of a bath or a bathe; the feeling of well-being; the recovery of weight; make these some of the most grateful surgical patients that exist. The alternative in many cases is loss of weight until the patient is skin and bone, the presence of sinuses, skin abscesses, the day and night rest disturbed by constant bowel action and possibly the onset of malignancy after some years.

Q.T. (*Great Britain*).—Following the example of the United States, the British colostomy patients have formed a club: 'Q.T., G.B.'. From this organization information on all the recent advances in bags, rubber, straps, gum, can be obtained, and in matters of this sort the patient can give much better and more practical advice than the family doctor. In this disease even more than any other there appears to be a particular camaraderie. These clubs or associations of diseases seem to be on the increase. We have now Alcoholics Anonymous, the Multiple Sclerosis Society, the Hæmophilic Association, the Guinea-Pig Club, and so forth. In Britain they have not gone so far as on the other side of the Atlantic where in certain parts of the States they have a society where members with a five-year cancer 'cure' wear a small gold sword as a badge. It is interesting to see that the era of Victorian prudery has swung almost to one of exhibitionism.

URINARY DIVERSION

For many years the operation of choice for urinary incontinence was to divert the urinary stream into the lower bowel leaving the patient with a cloacea—or common reservoir—but with control. The result of this operation invariably meant attacks of ascending renal infection. In some cases these were sufficiently mild for the patient to lead a useful life and even bear children but in others the attacks were frequent and so severe that gradually destruction, complete or incomplete, of one kidney or both kidneys took place. The results of this operation have varied greatly depending upon whether the patient was operated on as a child for ectopia vesicæ or other congenital deformity or in adult life for malignant disease or other destructive lesion of the bladder. More recently two alternatives have become common practice. They both reduce the danger of the ascending infection at the price in the one case of a fæcal fistula and in the other of a urinary fistula.

In the first a colostomy is performed in the left iliac fossa and the ureters are transplanted into the lower, now empty and in time sterile, bowel, and continence both day and night is perfect by means of the anal sphincter. In the second case, a portion, perhaps 12 to 18 inches (30 to 45 cm.), of lower ileum is detached from the main portion of the small intestine. The small intestine is resutured in continuity and the isolated sausage of ileum has one end closed and the other brought to the surface and into this the two ureters are implanted. Naturally the open end projecting from the

surface of the abdominal wall is covered with a Rutzen bag and obviously no sphincter or other control is available. 'Micturition' will be a continuous process, evacuation being the result of peristalsis and different from the effective action of the detrusor action of the bladder. The urine will be sterile, although cloudy due to the mucus of the intestine and, as stasis does not occur in the loop, the absorption of electrolytes across the surface of the gut is almost negligible. Thus the patient can now be offered three alternatives: (i) no external opening with the rectum acting as bowel and bladder, with ascending infection to an unpredictable degree almost a certainty; (ii) he becomes a colostomy patient with colon and rectum becoming a continent bladder and infection no longer a problem; (iii) he can retain normal bowel apparatus and wear for ever a bag over the ileostomy bladder. The Rutzen bag will be emptied by stopcock four to five times a day. A large bag can be fitted for longer periods. The average man can empty the bag in the ordinary public lavatory without any embarrassment. The small bag can be detached at any time and a fresh one replaced and once a week or so the adhesive ring which holds it to the abdominal wall will be detached and reapplied. The patient should be able to lead an ordinary life with games of all sorts—perhaps pushing in a rugby scrum should be avoided! Infection will not occur and the price of safety will be not only eternal vigilance but the wearing of a well-fitting bag.

OTHER USES OF THE ISOLATED ILEUM

Much use and abuse have been made of this tolerant and unsuspecting piece of alimentary canal. It has been made to replace the renal pelvis, and the ureter (one or both), and it has been superimposed on the contracted bladder rather like a second storey in a modern house to give increased accommodation. This has proved of great value where, for instance, in advanced but healed cases of tuberculous disease of the bladder, the patient has been left with a minute bladder (thimble bladder) and intense frequency from mechanical reasons makes life impossible by day and by night. To add this annexe to the bladder gives extra room. It does, however, require a normal trigone and base to the bladder with normal sphincter control. The patient must remember that the urine will always be cloudy in proportion to the area of mucous membrane in the additional bladder and that total or treble micturition may be necessary to evacuate the bladder, as actual micturition itself will be by the detrusor mechanism of the bladder but the second bladder will have to fill the basal bladder if this is to take effect. The new bladder naturally cannot work in direct conjunction with the sphincter machinery.

Isolation of the cæcum and terminal ileum with implantation of the ureters into the cæcum appeared at one time an attractive proposition. The terminal ileum was made to project through the abdominal wall and the whole new bladder looked rather like a teapot with spout. Although the ileo-cæcal valve gave the patient a closed and continent bladder, relief

could only be obtained by the passing of a catheter along the stump of the terminal ileum which naturally made the method no longer practical politics.

CARDIAC SURGERY

The present, or third, phase of cardiac surgery is certainly the most interesting, and when the technical problems have been settled it will allow more detailed and definitive surgery to be carried out.

(1) Phase one was surgery on the actively beating heart, with routine chest anæsthesia. This allowed extra-cardiac anastomoses and ligatures to be carried out as well as rapid intracardiac dilatations. In this phase ligation and/or section of the ductus arteriosus, excision of coarctation of the aorta, right atrial valvotomy, as well as the various great-vessel anastomoses designed to by-pass obstruction, were the most common surgical procedures.

(2) In phase two, under refrigeration anæsthesia the metabolism of tissues generally and the brain in particular can be reduced to the state of a hibernating animal, and the heart beat can be occluded for seven to eight minutes. This allows certain intra-cardiac operations, particularly the closure of septal defects, to be carried out.

(3) In phase three the venous return to the heart is diverted through an extra-corporeal heart-lung apparatus so designed that the circulating blood is returned fully oxygenated to the body to circulate through the body and supply its splanchnic and somatic needs. Among the heart-lung machines now in use are the Melrose machine in England, the Lillehei in the United States, and the latest on the market comes from Sweden. Oxygenation can be obtained by bubbling in suitable amounts of oxygen or else introducing the oxygen across a surface film thus simulating the normal lung alveoli. Such technical difficulties as temperature, quantity, clotting, speed, infection, pyrogens from the apparatus, and damage to the red cells, all become at once evident, and the evolution and perfection of a safe and simple machine is being investigated in many centres. With this technique the silent heart, fully open and quite dry, can be operated upon and surgical closure of a defect can be obtained under direct vision without hurry and with meticulous precision not possible before.

ARTERIAL PROBLEMS

'L'homme a l'âge des artères' is an aphorism that is as true today as it was when first said by Ambroise Paré in the sixteenth century. But it was hoped that when man could be supplied with new arteries from the cadaver or with nylon replacements this statement might no longer be true. In general terms lesions of the healthy artery wall such as embolism (from a distant source) or trauma react well and permanently to immediate surgery: not only is the wall itself healthy but the collaterals are competent. On the other hand, in the patient with the arterial system diseased in all its parts, peripheral, coronary, intestinal or cerebral, a localized lesion can be repaired only with a hope of temporary alleviation. Any tubular replacement of the resected artery, be it cadaver artery or nylon tube, will only remain a patent

tube so long as an adequate forceful stream is circulating through it. The lumen may develop a fibrinous smooth type of lining but no genuine endothelium can be expected. In arteries as small as the common femoral, as found distal to Poupart's ligament, the lumen is too small, the *vis a tergo* insufficient and most arterial grafts in this region in time become thrombosed. A slow thrombosis, however, can give the collaterals time to enlarge and compensate and so the graft can in certain cases be said to have served a useful purpose. In the abdominal aorta, with its wide lumen and its more forceful current, a good result can be expected and in many cases it is at some distant point of the arterial system that the final calamity arises. To remove a clot can be effective if the artery wall is soft and pliable and healthy. Often such clots have not arisen locally but from the heart or some distant source. They differ greatly from the organized clot which arises primarily at the seat of obstruction and whose removal entails an endarterectomy leaving a tube with a rough lumen and one most prone to recurrence of thrombosis. By-passing of the local obstruction by using a suitable vein, e.g. the long saphenous, can be most effective. One must remember to reverse the direction of the vein, to ensure that the valves are opening in the right direction.

AORTOGRAPHY

Now that a safer technique has been evolved, aortography has become more popular. To inject the artery blindly through the lumbar region was followed in some cases by serious complications. In some cases the needle displaced a plaque from the wall of the artery; in other cases the needle having entered the aorta emptied the entire contents of the syringe into an outgoing vessel on the opposite wall, for instance the opposite renal artery, so that this small vessel received for itself what was intended for the aorta. The result was necrosis of the organ supplied. In other cases the needle before reaching the artery has damaged the blood supply to the colon with consequent sloughing of that viscus. More recently the method of passing a catheter from the femoral artery in the groin and then injecting when the tip of the catheter has reached a selected point in the abdominal artery has proved much less dangerous and more effective. A recent modification of this is where the catheter has a curved end and, when in the aorta, the point of the catheter can be made to enter the selected vessel, for instance the right or left renal artery, and subsequently the correct dosage required for that particular organ injected into its own artery. Frimann Dahl, of Oslo, has perfected this technique and certainly his results are most impressive, showing the individual selection and detail that can be obtained.

CONCLUSION

These are but a few of the interesting problems which an enlarging surgical vista is bringing into perspective.

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ADVANCES IN OBSTETRICS AND GYNÆCOLOGY

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Although investigation and therapy of the three main maternal hazards in obstetrics—toxæmia, hæmorrhage and infection—are still one of the main objectives of the medical profession, the dramatic improvement in care of patients suffering from these conditions over the past twenty years has permitted a reorientation of interest in obstetrics so that a greater concentration has been possible on the less morbid and more psychological aspects of maternal care such as infertility, interest in the growth and development of the previable and viable fœtus and maternal or prepared childbirth programmes. Obstetrics therefore may be considered as a subspecialty which concerns itself with the origin of the embryo as well as its ultimate delivery as a full-term fœtus, and problems of infertility, early and late abortion may thus be considered under this heading.

INFERTILITY

There is a gradually growing impression that the multitudinous varieties of therapy, hormonal and otherwise, which have been used for male and female infertility in the past have actually had little to do with success or failure in terms of subsequent pregnancies.

A collective series of 9,595 married couples from various environments and economic groups discloses the fact that 65 per cent. of wives are pregnant at the end of six months of attempted conception, 81 per cent. at the end of one year, and 90.5 per cent. achieve a pregnancy within two years (Buxton and Southam, 1958). This means that the length of time during which pregnancy is attempted must be considered in the treatment of any infertility case because an appreciable number of patients will become pregnant regardless of treatment, depending upon the length of time of attempted pregnancy. Furthermore, from the same clinic it was ascertained that about 20 per cent. of the ultimately pregnant patients became pregnant within the first month to six weeks after their first infertility clinic consultation; in other words, before they could have received any appreciable amount of therapy unless the initial history and physical examination could be considered as a therapeutic procedure. This not infrequent incidence of pregnancy following an appointment to visit an infertility clinic or shortly thereafter has been commented on by many other authors, including Bishop (1953). Jeffcoate (1954) considers the entire subject of infertility, including therapy, 'to be obscured by clouds of fantasy, wishful

thinking, false promise and quack remedy as much today as it was in the days of love potions and fertility amulets'. The future therapy of infertility will depend largely, not on the somewhat uncritical clinical *post hoc* research investigation, but more on the basic fundamental research being carried on in preclinical laboratories at the present time throughout the world.

ABORTION

'Abortion' is a diffuse word with many implications, and the therapy of certain types of abortion is sometimes quite different from, in fact occasionally diametrically opposite to, other types of abortion. The various types of this condition will therefore be considered briefly and separately.

'THERAPEUTIC ABORTION'

A 'therapeutic abortion' is an induced abortion carried out legally when adequate medical consultation indicates that continuation of the pregnancy would endanger the woman's life or, in some localities and countries, seriously endanger her health and welfare. Since the now famous Bourne case in England in 1939 (Rex v. Bourne, 1939) the so-called 'Offences Against the Person Acts' permitting legal abortion in England have been somewhat liberalized, but in both England and the United States legal abortion for any but very stringent medical reasons is rarely permitted. Since medical indications for therapeutic abortion are rapidly diminishing there is considerable social pressure for further liberalizing of psychiatric and socio-economic indications for legal termination of pregnancy. To assist in what Guttmacher has aptly described as the 'doctors' dilemma', therapeutic abortion committees have been established in many hospitals in both the United States and England. The aim of these committees is not only to prevent indiscriminate use of this technique of population control, but also to permit abortions which are legally and medically advisable.

In the Margaret Hague Hospital in Jersey City, for instance, only eight therapeutic abortions were carried out in the last 140,000 deliveries, and the hospital has still maintained in the last 56,000 deliveries a maternal mortality of less than 1 per 1000. There are no therapeutic abortions permitted in the National Maternity Hospital in Dublin, yet a recent report on their maternal mortality statistics in cases of heart disease complicating pregnancy compares favourably with that of institutions where therapeutic abortion for this condition is not uncommon (O'Driscoll, Barry and Drury, 1957). It is significant that comments from both these hospitals as well as elsewhere indicate that their success in treating medical complications of pregnancy depends not infrequently upon prolonged medical care, sometimes even requiring bed rest throughout almost the entire period of pregnancy, to say nothing of possibly several months thereafter. Naturally this is not economically feasible in most circumstances, but it does indicate that, unless socio-economic conditions are

taken into consideration, the real medical indications for therapeutic abortion are slim indeed.

On the other hand, therapeutic abortion for fœtal indications is increasing somewhat because of the discovery of fœtal abnormality due to maternal rubella in early pregnancy, for instance, and Rh and possibly blood-group incompatibilities in parents. Recent studies (Krugman and Ward, 1958) indicate that the risk of congenital malformation resulting from a first trimester pregnancy complicated by rubella is about 10 to 12 per cent. These authors strongly recommend that 'all pregnant women with no previous history of rubella be given at least 20 ml. of gamma globulin intramuscularly in the first trimester as soon after exposure to rubella as possible'. This may well prevent the onset of the disease and thus eliminate the possibility of fœtal abnormality, although it cannot be denied that in very occasional cases the administration of gamma globulin does not prevent the viræmia from occurring, but only prevents the rash from appearing, thus creating a false sense of security. It is therefore not uncommon in the United States for hospital abortion committees to permit therapeutic abortion in this type of case. Termination in the presence of persistent erythroblastosis when the male parent is homozygously Rh positive, or persistent occurrence of other congenital anomalies in offspring, is also not infrequently permissible in the United States.

SPONTANEOUS ABORTION

Since a large percentage of early spontaneous abortions are due to trophoblastic abnormality, it may well be advisable to attempt no treatment of the early threatened abortion because, if treatment is successful, which it probably will not be anyway, it may only delay an inevitable abortion which would have been much less serious if it had occurred sooner. Therefore, unless the patient has been attempting pregnancy for a long time, and has great difficulty conceiving, or unless she is an habitual or recurrent aborter, probably the best therapy for this condition is none at all.

Unfortunately, there are few forms of therapy which seem to be particularly successful. Recent studies on pregnanediol excretion following different types of therapy for threatened abortion have confirmed the impression of many that the concentrated stilbœstrol therapy described by Smith and Smith (1948) has not proved to be particularly efficacious. On the other hand, the administration of large amounts of progesterone or progesterone-like substances has resulted in increased pregnanediol output and may thus possibly be of some therapeutic value. The amount of progesterone when given by mouth must be large, however—from 50 to 100 mg. daily being advised in early pregnancy. The status of the 'progesterone-like' substances sometimes called '19-nor progestational steroids' may be of some value when administered in equivalent amounts.

Trophoblastic and fœtal salvage in the 'habitual aborter' is likely to be a more complicated process and treatment depends upon the reason why

the patient habitually aborts. If basic progesterone deficiency has been identified by pregnanediol determination or vaginal smear, large amounts of progesterone intravenously may overcome the endogenous failure of progesterone production (Randall *et al.*, 1955).

Since it is obviously most important to determine the etiology of habitual abortion before therapy is instituted, an examination of the patient between abortions is a vital investigative procedure. Not uncommonly, congenital abnormality of the genital tract such as bicornuate or didelphate uterus (occasionally only identifiable by hysterography) may be the cause of habitual abortion. In this case operative repair of the defect as carried out, for instance, in the Strassmann procedure, may permit subsequent full-term pregnancies. Another possibly congenital condition which is an occasional cause of late habitual abortion, or early and frequently non-viable prematurity, is what has come to be known as the 'incompetent cervix'. This condition may occasionally be identified between pregnancies by hysterography, but is more often and accurately diagnosed during pregnancy by a fairly rapid and progressive effacement and dilatation of the cervix during the second trimester or as early as the 10th or 12th week. Surgical correction of this condition is carried out very satisfactorily by the technique of placing a heavy purse-string suture, either of fascia lata or non-absorbable material, around the cervix at the level of the internal os beneath the vaginal mucous membrane at about the 12th to 14th week of pregnancy. Details of this type of operation are described by Barter *et al.* (1958). As these authors suggest, before carrying out this procedure it is most important to be sure that the diagnosis is correctly made, because this type of therapy is unsuccessful in cases in which late miscarriage or early prematurity occurs with an unexplained spontaneous onset of active labour pains.

PRE- AND POST-MATURITY

One of the major causes of perinatal mortality is prematurity but, apart from its connexion with other pathological conditions of pregnancy such as toxæmia, placenta previa, and accidental hæmorrhage, it is largely unexplained. The treatment of prematurity therefore, except for the treatment of other etiological conditions predisposing to it, is largely empirical. Enthusiasm for the use of relaxin in an attempt to stop premature labour has been tempered somewhat by the finding that, although this substance may decrease the strength and frequency of uterine contractions, it also has a tendency to relax the cervix so that not infrequently the purpose for its administration is counteracted by this latter effect. The probabilities are that the best treatment for the unexplained onset of premature labour is bed rest and adequate sedation.

There is an interesting and certainly not unanimous divergence of American and British opinion concerning postmaturity. The fœtal oxygenation studies of Turnbull and Baird (1957) in Scotland confirm the impres-

sions of the dangers of prolonged pregnancy described by Kloosterman (1956), Browne (1957), and others in England and on the continent. In the United States, however, there have been somewhat different clinical and laboratory findings in connexion with postmaturity (Buxton, 1957; Stewart, 1952). Whether or not the postmature patient should be delivered, either by induction or even Cæsarean section, is undecided, but it is the majority obstetrical opinion in the United States that the added obstetrical hazards of induction and Cæsarean section, plus the as yet somewhat questionable validity of the greatly increased infant mortality due to postmaturity, suggest the advisability of conservative measures in connexion with this condition.

TOXÆMIA

In spite of some evidence to the contrary (Robinson, 1958) the consensus of opinion is that one of the basic necessities in the treatment of toxæmia of pregnancy is the elimination of excessive sodium and fluid from the toxæmic patient. Since many of the common diuretics in use are likely to produce acidosis on prolonged administration, the use of chlorothiazide, a non-acidosis-producing diuretic, has been found most satisfactory. The usual dosage is 500 mg. twice daily for five days, omitting the medication for two days (e.g. over the weekend) and then resuming therapy again.

There is no question but that the greatest safeguard against toxæmia is careful and continuous antenatal care from as early as possible in pregnancy to the time of delivery. Office visits once a month during the first two trimesters, twice a week during the last trimester, and once a week during the last month have probably done more to reduce maternal and infant mortality from toxæmia than any other single factor. During these visits suspicion of toxæmia should always be kept in mind. Solicitation of symptoms, blood-pressure readings, examination for œdema, hyperreflexia, sudden weight gain and urine analysis are all important—in addition to the evaluation of the size and position and condition of the fœtus. Persistent blood pressure readings of 130/90 mm. Hg or over, plus any other toxæmic signs or symptoms, should immediately place the physician on guard; the patient should be given daytime sedation and be required to rest; salt should be withdrawn from her diet and, if any œdema is present, chlorothiazide should be administered in the dosage already described.

Should the toxæmia develop into pre-eclampsia, or should the patient be first seen in a pre-eclamptic stage, she should be admitted immediately to hospital for complete rest and further therapy. Since there is evidence that the administration of barbiturates decreases cerebral blood flow, and since one of the objectives of therapy is to decrease cerebral œdema, it is probably inadvisable to use barbiturates for sedation in pre-eclamptic toxæmia. Adequate sedation, as well as additional diuresis, may be obtained by the administration of magnesium sulphate, 10 ml. of a 20 per cent. solution intramuscularly every four hours, or even in greater concentration and quantity if necessary. In cases of severe hypertension the use of hypo-

tensive drugs such as reserpine, hydrallazine, or veratrum alkaloids may be used by mouth or, in severe cases, by continuous intravenous drip. The use of these drugs is a delicate procedure, however, and should not be undertaken by anyone who has not had considerable experience in their use. Sudden hypotensive crises, renal shutdown, and even fœtal death may occur as complications. When properly used, however, these drugs are of great value in controlling the severely hypertensive toxæmic patient.

HÆMORRHAGE

Establishment of blood banks has been invaluable in preventing mortality from obstetrical hæmorrhage. One of the recent problems involving uncontrollable hæmorrhage, however, is afibrinogenæmia. This condition produces continuous bloody oozing from the uterus or from any cut surface (such as might occur in the postoperative Cæsarean incision, for instance), bleeding from gums and other mucous membranes and subcutaneous petechiæ. It occurs in desperate obstetrical situations where there is likely to have been extravasation of blood within the myometrial tissue, such as accidental hæmorrhage or premature separation of the placenta, for instance, and also in cases of intrapartum fœtal death prolonged for more than a few weeks. Afibrinogenæmia should be carefully watched for in any of these obstetrical crises by observation of blood clot lysis in a test tube or by actual fibrinogen level determination if a laboratory is available. If clot lysis occurs in a test tube in one-half to one hour a condition of afibrinogenæmia may be strongly suspected. Therapy for this condition, of course, is the administration of fibrinogen if it is available, 1 g. usually being sufficient to control the condition but up to 5 g. occasionally being necessary. Should no fibrinogen be available, transfusion with fresh, not bank-stored blood, is the next best alternative. The patient with an intrapartum fœtal death should be carefully watched for signs of mucous membrane or subcutaneous bleeding and a clot lysis or fibrinogen test done weekly after the third week of intrapartum death. Should signs of afibrinogenæmia occur, fibrinogen replacement should be arranged for and the patient delivered as soon as possible. This is the only condition of which I am aware in which it is important to force delivery before spontaneous labour occurs in a woman carrying a dead baby.

INFECTION

Although the almost miraculous control of infection produced by modern antibiotics has reduced this once great hazard of osbstetrics to minimum proportions, the recent finding of antibiotic-resistant staphylococcal strains in nurseries and obstetrical wards as well as other hospital areas has recreated a danger which demands attention and control. Various sources have been implicated in antibiotic-resistant staphylococcus outbreaks. Hospital staffs, especially nurses taking care of babies in nurseries, may have been involuntary spreaders of the organism, and recently hospital

laundry and hospital cleaning techniques have been under suspicion (Hurst *et al.*, 1958). Should staphylococcus infections occur in the nursery or on the obstetrical ward, or anywhere else for that matter, it is most important to clean out the area as quickly as possible, wash it down with damp antiseptic solution and treat all patients with some variety of antibiotic which has not been used in the environment before. It may be that the antibiotic-resistant strain of staphylococcus will respond to one of the newer types of antibiotic with which it has not previously been associated. Parenthetically, hospital staphylococcus epidemics of this type are one of the best arguments against the indiscriminate and prophylactic use of antibiotics.

ANALGESIA AND ANÆSTHESIA

More analgesia and anæsthesia for labour and delivery is used in the United States than in Great Britain or other countries. In Great Britain therefore a warning in this respect may be largely unnecessary.

There is ample proof, of course, of the transfer of barbiturates (Ploman and Persson, 1957), as well as cyclopropane and other anæsthetics across the placental barrier. Every obstetrician who has had experience with the use of large amounts of barbiturates and any type of inhalational anæsthesia is accustomed to delivering sleepy babies. Whether or not perinatal mortality is increased thereby is a moot question, but there is enough suspicion of anoxia as a culprit in brain damage to try as much as possible to prevent respiratory difficulties in the newborn.

This is one of the reasons, although there are others mostly psychological, for the enthusiasm of recent training techniques to prepare mothers for childbirth so that they require a minimum of anæsthesia or analgesia. In a recent panel discussion on 'psychoprophylaxis' for childbirth at the Second World Congress of the International Federation of Obstetrics and Gynæcology held in Montreal on June 22, 1958, representatives from Great Britain, France, Germany, Switzerland, Russia and the United States were surprisingly unanimous in the objectives of childbirth preparation although the techniques were somewhat different. Continental opinion in general favoured the 'psychoprophylaxis' technique originated in Russia, which is said to use Pavlovian conditioned reflex methods in order to establish a condition of equanimity and even freedom from pain during labour. The British 'natural childbirth' techniques ably described by Arthur Bell as being a modification, and possibly a less spectacular variety, of the technique originally described by Grantly Dick Read, consists, as do the American 'prepared childbirth' techniques, of education and training of the mother and also to a certain extent the father. Labour and delivery may thus be entered into with anticipation and enthusiasm rather than dreaded anticipation of the unknown. Few would deny that techniques such as these are of great psychological benefit to many women, and it may be true that the amount of analgesia and anæsthesia necessary for delivery of these women is less on the average than with the untrained

individual. But whether or not these techniques are of actual obstetrical value in terms of obstetrical measuring units such as length of labour, percentage of traumatic delivery, perinatal mortality, and the like, is still a moot question.

GYNÆCOLOGICAL SURGERY

This article will not attempt to review the most recent changes in specific operative and radiation therapy techniques in the treatment of gynæcological cancer except to say that certain changes have occurred. These, however, are of interest to the specialist in gynæcological cancer surgery to whom all such cases should be referred.

Concerning gynæcological surgery in general, recent therapeutic changes have consisted more in trends than in dramatic new techniques. The advisability of total hysterectomy rather than the subtotal supravaginal type is now well established and the individual who carries out a supravaginal hysterectomy leaving the cervix *in situ* might well be accused of carrying out inept surgery unless there is some special reason for such a procedure. In the United States gynæcological surgery by the vaginal route has received considerable emphasis during the past few years and, although this technique has definite limitations, its advantages are many.

There is a controversy in the United States at the present time concerning the advisability of preservation of the residual ovary at the time of hysterectomy in the menopausal woman or the woman over forty. Possibly the reason for the controversy is that none of the enthusiasts on either side has much in the way of impressive finite facts with which to support his contentions. At one end of the scale is the point of view which expresses the idea that, were it not for the psychological implications involved, the hysterectomized woman has no use for any ovaries, and whatever œstrogenic replacement is necessary can easily be obtained in the corner pharmacy. Furthermore, removal of the ovaries in this fashion protects her against the possibility of future ovarian disease, either benign or malignant. The opposite opinion is that the post-menopausal ovary continues to secrete varying amounts of œstrogen which is invaluable to the physiological harmony of the post-menopausal woman and it is therefore physiologically as well as psychologically traumatic and harmful to remove the ovary in this type of patient. I have a definite inclination towards the former point of view, but am by no means completely convinced that it is correct.

OFFICE GYNÆCOLOGY

The advent of the Papanicolaou smear for cancer detection has been a valuable aid in the reduction of genital cancer. The present prevalent technique in the United States, as well as abroad, is to take not only smears of the cervical and vaginal epithelium but also aspirations of endometrial contents at least once a year in as many women as possible. The resultant cost in time, equipment, personnel, salaries and space for the detection of every unsuspected carcinoma of the cervix or corpus is great, but a life

cannot be measured in units such as these and the early detection of pre-invasive or stage I carcinoma is certainly a life-saving procedure.

One of the commonest complaints for which the woman consults the gynæcologist is vaginal discharge accompanied by unpleasant itching or burning which may even result in excoriation of the external genitalia. *Moniliasis* and *trichomoniasis* have long been known to produce this kind of condition and certain non-specific bacterial infections are occasional etiological factors. In 1955, a specific bacterial organism, *Hæmophilus vaginalis*, was described by Gardner and Dukes which produced severe vaginitis. The organism is not particularly difficult to culture and identify and an investigation for it should certainly be made in all otherwise unexplained cases of vaginitis. The treatment of this condition by the use of a triple sulphonamide cream has been highly successful.

Although many new remedies, both local and systemic, have been proposed for the treatment of vaginal moniliasis, none appears to be more satisfactory than that of thoroughly coating the entire vaginal mucous membrane and external genitalia with 1 per cent. aqueous gentian violet twice a week for three or four applications. Many new remedies, both local and systemic, have been suggested also for trichomoniasis but until some systemic therapy has been devised for treatment of both male and female this condition will probably continue to plague an appreciable number of women. Overtreatment with practically any medication is considered to be a not infrequent cause of therapeutic failure in this disease (Buxton and Weinman, 1957). The use of a pentavalent arsenic preparation (commercially prepared in the United States as 'powdex') in the form of a powder insufflation twice weekly, interspersed by dilute vinegar douches (one teaspoonful in a quart [1 litre] of warm water) appears to be about as efficacious as any other type of therapy.

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ADVANCES IN PÆDIATRICS

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To an increasing extent changes in clinical medicine depend upon knowledge derived from other fields; less and less are clinical investigations primarily responsible for therapeutic advances. Clinical research is now playing its main part in elucidating the causes and mechanisms of diseases which thus become more amenable to preventive and curative treatment. Clinical pædiatrics is no exception, and it is fortunate that pædiatricians in this country have steadfastly insisted that pædiatrics must not be permitted to become a separate specialty but should remain an integral part of the general body of medicine, surgery and public health. By this arrangement it has remained sensitive to the advances taking place in related fields. It also favours the diffusion of new ideas in a two-way sense, and other disciplines can be influenced by what is good in pædiatric thinking. The advances I shall discuss in this article depend upon knowledge derived from chemistry, psychology, pharmacology, medicine and surgery.

PSYCHOLOGICAL ILLNESS

Pædiatricians and other doctors are now giving as much attention to the psychological and emotional origin of symptoms as to psychological illness itself. Practitioners often deal with children with their various disturbances of conduct; these patients are regarded as 'ill' in terms of their emotional state. They are equally aware that the cause of many a symptom can be emotional in origin as well as physical, and that psychological factors often increase the disability of a physical illness, especially when it is a chronic one.

Child guidance and hospital psychiatric services have been provided on a considerable scale and at a large cost, but these were never intended to deal with all the emotional and psychological troubles which bring children to the doctor; nor would it be possible, or even desirable, that these sources should be expanded to cover all this work. Both the family doctor and the practising pædiatrician have their parts, and very important ones, to play in helping and advising about children who suffer from emotional disorders. Treatment must embrace the child's emotional environment, especially the parent-child relationship. Therefore it is seldom realistic to regard the child as 'the patient'; on the contrary 'the patient' really consists of a small group of individuals, the family, among whom emotional contacts and attitudes are faulty. Thus, the attitude of the parents towards the child may lack understanding or there may be a large element of rejection (often unconscious), over-protection or perfectionism. An improvement in these relationships must be the practitioner's aim. Sometimes the child may, himself, need some additional treatment, perhaps by a child psychiatrist.

PARENT GUIDANCE

Parent guidance has two sides: educational and psychotherapeutic (Katz, 1958). The first requires in the main common sense, experience, and wisdom; the second needs special knowledge and insight. Educational guidance seems a prime essential in many situations, and yet it often disappoints, however wise its content, because something else is needed. A mother can be so dominated by her feelings of anxiety about the child's bad behaviour, or resentment against him, or perhaps lack of self-confidence, that she is in no position to accept good advice or to act on it. She has first to be in control of her feelings and emotionally comfortable in her parental role; the same may apply to the father. Moreover, disturbed children often live in a home which is on the point of breaking up, or they have a parent, or parents, who are disturbed or unstable. In such circumstances psychotherapy has a place in the total treatment. Its scope and methods in general practice have recently been discussed by Balint (1957), Harrington (1957) and Katz (1958) whose writings, among others, will repay study. For such work the practitioner must exercise patience and skill in order to establish a satisfactory rapport; in this way he can often provide the necessary emotional relief. He needs to be a sympathetic and an understanding listener, not a critical one; he must provide support and reassurance without giving vain hope or empty promises. An understanding of the principles of psychotherapy will help him to succeed in tasks which are often difficult and always take up a good deal of time. But he must also know himself as well as his own limitations in psychotherapy and be prepared to work within them.

CHILDREN IN HOSPITAL

Pædiatricians and nurses now recognize that they can play an important part in mitigating the drawbacks, psychological and otherwise, of a child's admission to hospital and that admission can often be avoided by thoughtful planning. In Britain we are attending to many details which make for happiness and welfare during a stay in hospital. Ideas are often more compelling than facts, and the present moves to humanize a child's stay in hospital are largely due to the inspiration of the late Sir James Spence (1947) who, only a few years ago, was openly deploring the over-rigid institutional atmosphere of most pædiatric wards and advocating less discipline, less tidiness and more humanity. The present interest in the welfare of patients in hospital is a happy feature of British pædiatrics and one which favourably impresses the discerning visitor to Britain.

There is now fairly general agreement that admission to hospital usually occasions some emotional stress, largely on account of parental separation, although actual damage does not necessarily ensue; but, generally speaking, the younger the child the more probable are the ill-effects and these effects may well be a threat to his developing personality. A child's removal from home for admission to hospital does not, of course, always lead to a significant emotional disturbance. Just as it would be a fallacy to conclude

that, because a 2-year-old child is miserable and disturbed in hospital, all children of similar age will be affected in the same way; so, too, would it be wrong to conclude that because the majority of patients in a well-run children's ward are happy during their stay and show no disorder of behaviour afterwards, this experience is always harmless. Clearly it is advisable to act with care and understanding, and it may be wise and possible to postpone admission, as in the case of an elective operation, until a child is of an age when the immediate presence of the mother is less important to him.

That the welfare of hospital children is a current problem is illustrated by the setting up of a special committee by the Central Health Services Council which will soon issue its report. Practical proposals aimed at mitigating the drawbacks, and helping the individual child during his stay, have been submitted to this committee by members of the British Pædiatric Association, and these will be published shortly under the title of 'Welfare of Children in Hospital'. Meanwhile, Robertson (1958) has reviewed some of the problems. The Department of Child Health at Guy's Hospital has recently issued a pamphlet ('Billy Goes to Hospital') for child patients, and a companion pamphlet to help the parents in preparing the child for his experience.

Among the various proposals suggested, the most radical preventive step is that of avoiding admission altogether, which is often possible. This is largely in the hands of the practitioner, but the Home Care Scheme for Sick Children operated at St. Mary's Hospital (Lightwood, 1956; Lightwood *et al.*, 1957) has shown what the hospital can do to help the practitioner in an urban setting and the same has been indicated by Gairdner (1957) for rural areas. In certain cases it is a good plan for the mother to tend her child in hospital, suitable accommodation being needed for this. Daily visiting should be encouraged while a child is in hospital. In Britain not so many years ago visiting once a week was thought to be enough. Guy's Hospital was the first teaching hospital to encourage daily visits to the children's wards. St. Mary's Hospital quickly followed and soon tried the plan of 'unrestricted' visiting in which the parents are encouraged to visit their child at their convenience, except at rest time. Difficulties were expected in this trial and some were anticipated by appropriate rules; but the difficulties were less than expected and the trial was successful. Such access by the parents affords the best opportunities for mutual knowledge and respect between staff and parents, and the necessary medical information is readily given.

With appropriate accommodation and equipment there are, of course, many ways in which, by the use of patience and imagination, the pædiatric staff can remove feelings of strangeness and a child's fears. If medical and social conditions permit, home is the best place for the sick child to be nursed, in his own familiar surroundings, but when admission is necessary much can then be done to make it an experience to be enjoyed.

PHENYLKETONURIC OLIGOPHRENIA

The pathogenesis of many disorders affecting children has in recent years been explained, wholly or in part, by chemical and metabolic methods, as for example, galactosæmia, cœliac disease and phenylketonuric oligophrenia. In each of these conditions the metabolic findings have indicated a logical form of treatment. Phenylketonuria may be taken as an example. First described by Fölling in 1934, it is due to an inborn metabolic error inherited as a recessive character. The defect lies in an inability to metabolize the amino-acid, phenylalanine, as a result of the absence from the liver cells of the enzyme, phenylalanine hydroxylase. The simplest hypothesis is that the gene normally responsible for the synthesis of this enzyme is replaced by a mutant gene incapable of this synthesis. The severe mental deficiency that results is thought to be due to the accumulation of phenylalanine in the blood with consequent intoxication by this amino-acid. The logical treatment and, in fact, the only form of treatment so far suggested, is to give a phenylalanine-free diet, and this has now been done by a number of workers with varying degrees of success. The effects of this metabolic disorder begin to operate at or soon after birth; little therefore can be expected from the treatment unless it is begun early in life.

Failure to metabolize phenylalanine causes the excretion in the urine of phenylpyruvic acid, a breakdown product of phenylalanine. Its presence can be detected in the urine by testing a fresh specimen with a 5 per cent. solution of ferric chloride. With this reagent phenylpyruvic acid gives a green or greenish-blue colour after standing for about three minutes. Without this test the condition cannot be diagnosed. Many of the affected patients are mentally deficient children with small heads and fair hair, but it would take an alert clinician to make the diagnosis unless he were on the look-out for it or without having the ferric acid test done on the urine in all cases of mental deficiency.

Woolf and his colleagues (1958) give details of a phenylalanine-free diet. It is a costly diet but the expensive items can be provided under the National Health Service. The most satisfactory results will be when the diagnosis is made in early infancy and the treatment not only promptly instituted but maintained afterwards without interruption. In order to make this feasible it should become a practice to test every infant's urine at the age of three weeks with the ferric chloride solution. The test should also be repeated at the age of three months because it has been shown that occasionally phenylpyruvic acid may be absent from the urine during the early weeks of life but present later. The urine of a sibling of a known case of phenylketonuria should be examined daily from birth. It has been calculated that, by means of such routine testing, there would be the possibility of detecting and treating between 20 and 40 new cases in Great Britain alone. This would be a small but significant contribution to the prevention of mental deficiency.

When a patient does not present until late in childhood the results of treatment are likely to be poor. A child's mental grading may be improved

only by a rise from the idiot to the imbecile level. Woolf and his colleagues consider that treatment is worth instituting if a child is under 2 years old and has a general quotient (G.Q., Griffiths scale) of not less than 20, at 3 years with a G.Q. of not less than 30, at 4 years with a G.Q. of not less than 40, and so on.

PRIMARY TUBERCULOSIS

Since chemotherapy against tuberculosis has become available the declines in the mortality and the morbidity rates have been accentuated and the possibility of controlling tuberculosis has come much nearer. The incidence of primary tuberculosis has also been reduced as a result of the much smaller number of adult cases with positive sputa and the wider use of BCG.

When primary tuberculosis is diagnosed a decision has to be taken as to whether or not chemotherapy should be used, and the indications are not altogether clear because there is no satisfactory proof that the lesions of the primary complex can be radically influenced by chemotherapy in the same way as the lesions of adult pulmonary tuberculosis. The most obvious benefit is that hæmatogenous lesions are very unlikely to occur while chemotherapy is being given and the risk of meningitis is virtually removed. As miliary tuberculosis and meningitis show their greatest incidence in children infected during the early years of life (especially under the age of three years), and as meningitis usually develops within three or four months of the date of primary infection, it is generally considered that all cases under the age of three years should receive chemotherapy. From the age of puberty it has been shown that the risk of progressive pulmonary tuberculosis increases and therefore at this age chemotherapy is also employed. In the case of children with primary tuberculosis between these ages the indications for treatment are not generally agreed. Some authorities consider that all cases should be treated, some treat only cases with radiological signs, whilst others reserve chemotherapy for those children in whom the lesions are found to be progressive. The results of properly conducted chemotherapeutic trials are required to show which is the correct policy. Such trials are difficult to arrange and final results cannot be available for some years.

The fact that chemotherapeutic agents do not readily penetrate avascularized lesions, such as caseous broncho-pulmonary glands, is probably the chief reason why the results of treatment have so far been inconclusive. Isoniazid is the most powerful, soluble and diffusible of the anti-tuberculous drugs: it can enter living cells and kill intracellular bacilli. Streptomycin and PAS are less powerful and less diffusible. Examination of histological material shows that it is difficult to sterilize certain types of tuberculous lesions. Nevertheless, chemotherapy seems to be helpful in many cases of primary tuberculosis and removes most of the anxieties attendant upon the risk of dissemination.

SURGERY OF PRIMARY TUBERCULOSIS

Since it is known that chemotherapy may fail to control the caseous glandular lesions which may result from primary tuberculosis, there are certain

patients with such lesions for whom additional treatment may be required. For this reason surgery is now beginning to play the same sort of role in the treatment of caseous broncho-pulmonary glands as it has been playing in the treatment of caseous cervical glands. Surgical treatment has also been rendered safer by the use of chemotherapeutic cover.

The precise indications for surgical intervention have not yet been worked out. In the hands of a good thoracic surgeon the risks of operation (excision or evacuation of caseous gland) may be less than the inherent risks of a large and potentially dangerous caseous lesion lying in relation to a major bronchus. Selection of cases for surgery is important. According to Chesterman (1957), the following may be regarded as indications for surgery:—

(1) Perforation of the trachea or a major bronchus causing acute respiratory embarrassment (the majority do not cause a serious episode; when they do, immediate aspiration through a bronchoscope can save life).

(2) Perforation into a large bronchus which causes recurrent obstruction; this requires excision of the glands and suture of the perforation.

(3) Glandular pressure causing bronchial obstruction and pulmonary collapse which lasts more than four weeks; this requires excision of the mass or, failing this, incision and removal of the contents. There is a special indication when the right paratracheal glands are responsible and excision should not be delayed too long because glands in this situation are apt to lead to hæmatogenous dissemination, pulmonary tuberculosis and occasionally endurative mediastinitis with superior vena-caval obstruction.

(4) Glandular pressure which causes fibrous bronchial stenosis; this requires resection of stricture with anastomosis if possible, and sometimes resection of pulmonary tissue.

The surgery of primary tuberculosis is largely aimed at the relief of tracheal and bronchial obstruction and the effects of ulceration by caseous glands, and also towards preventing the destruction of pulmonary tissue; in contrast, the surgery of pulmonary tuberculosis concerns itself with the resection of portions of tuberculous lung. The surgical treatment of intrathoracic glands is only being undertaken in a few centres and many authorities consider that non-surgical treatment offers equally good prospects of cure. The selection of cases for operative intervention needs to be preceded by bronchography, bronchoscopy and, in certain cases, tomography.

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ADVANCES IN THE TREATMENT OF SKIN DISEASES

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THE chronicler of the new streams of knowledge that yearly are added to the whole is at once conscious of the vast amounts of material available, some apparently more important than others. In this respect John Brown (1900) quotes the profound remark of that 'prince of practical physicians', Thomas Sydenham: 'All professional men labour under the disadvantage in not being allowed to be ignorant of what is useless!'. This I have tried to avoid. Equally relevant, however, is Latham's remark to students at St. Bartholomew's Hospital: 'In entering this place, even this vast hospital, where there is many a significant, many a wonderful thing, you shall take me along with you and I shall be your guide. But it is by your own eyes and your ears and your minds and (I may add) by your own hearts that you must observe and learn and profit. I can only point to the objects, and say little else than: "See here and see there" '.

SWEATING AND ANTI-CHOLINERGIC DRUGS

The types of sweating include thermo-regulatory, emotional-hypothalamic, or neurogenic; the latter may be cholinergic or adrenergic (de Takats, 1957). Whilst sedatives help emotionally produced sweating, cholinergic sweating is reduced or abolished by atropine or the synthetic anti-cholinergic drugs. These include methanthelinium bromide ('banthine'), propantheline bromide ('probanthine'), hyoscine methobromide ('pamine'), adiphenine hydrochloride ('trasentin'), and others with long action, such as diphemanil methylsulphate ('diphenatil'). Side-effects are dryness of the nose and mouth, with a bitter taste, gastric disturbance, constipation or tachycardia. The drugs should not be given to patients with angina, and both urinary retention and increased intra-ocular pressure can occur, with paralysis of the pupil sphincter. Their uses in dermatology include essential hyperidrosis, dysidrotic pompholyx (cheiropompholyx), 'prickly heat', miliarial eruptions in atopic eczema or in eczemas affecting the easy sweating areas of hands, feet, groins or flexures; in occupational dermatitis where temperature or physical work may precipitate relapse through excessive sweating in the convalescent skin; in some cases of rosacea; in repeated furunculosis and pyogenic or fungal infections in moist areas and in ano-genital pruritus associated with sweating.

Neomycin, used locally, inhibits the offensive axillary odour resulting from bacterial action or apocrine sweat (Shelley and Cahn, 1955), and has been used in lotion form for prickly heat (Lyons and Hunt, 1955), possibly

influencing staphylococcal infection which may cause sweat-orifice obstruction.

TOPICAL HYDROCORTISONE

Increasing experience, combined with the need for economy, indicates that a 1 per cent. strength of hydrocortisone is adequate whilst 0.5 per cent. is often successful, although initial concentrations recommended have been as high as 2.5 per cent. (Staff of St. John's Hospital, 1957). Fludrocortisone 1 per cent. (Portnoy, 1958), or prednisolone 0.5 per cent. (Sloane, 1957) is equally effective, whilst hydrocortisone and hydrocortisone diethyl amino-acetate may be effective antipruritics in strengths as low as 0.25 per cent. or 0.1 per cent. (Lawrence, 1958). The best results appear in contact dermatitis, eczemas of the eyelids or external auditory meatus, circumscribed lichen simplex chronicus (neurodermatitis) and in pruritus ani et vulvæ. It is not recommended for widespread eczemas, and chronic cases probably respond as well to tar preparations. Many relapses occur up to two to six weeks after initial improvement (Vilanova, 1957) or often after a few days, as a rebound phenomenon when the treatment is suddenly stopped. Considered from the economic viewpoint it may be difficult to get patients off treatment once it is started.

Intolerance and increased irritation are usually related to the base which may contain free and sulphated higher alcohols capable of producing dermatitis (Sams and Smith, 1957); greasy bases suit thinner skins, whilst non-greasy ones are better on the easy sweating areas in groins, axillæ or arm-bends. Atopic eczema (Besnier's prurigo) shows unpredictable tolerance (von Kalz and Scott, 1956) to one type or the other.

Justification for combining such antibiotics as neomycin and oxytetracycline with hydrocortisone may exist for control of secondary infection, or to obtain increased anti-pruritic effect in ano-genital pruritus. Cowhage (itching powder) contains a proteolytic enzyme (Shelley and Arthur, 1955) capable of attacking proteins and releasing a chemical stimulus for itching. The itching sensation has been experimentally produced by introducing micro-quantities of proteolytic enzymes into human skin (Shelley and Arthur, 1957). Antibiotic-hydrocortisone combinations may therefore inhibit itch-producing proteases which are released by organisms on eczematous skin. Contact dermatitis, however, may occur from such added antibiotics, which, in the case of neomycin, may be overlooked as being a delayed tuberculin type of reaction (Epstein, 1956) rather than dramatically eczematous. Coal-tar extracts added to hydrocortisone may have a synergistic effect (Clyman, 1957); reduction of hydrocortisone concentration may be possible with consequent lowering of cost.

SYNTHETIC CORTICOSTEROIDS

Prednisone and prednisolone are employed more than cortisone and corticotrophin in control of systemic lupus erythematosus, pemphigus, exfoliative dermatitis or exfoliative psoriasis, intractable atopic eczema, and severe

erythema multiforme (Stevens-Johnson syndrome). The same adverse effects of prolonged dosage occur as with cortisone, but sodium retention is less of a hazard.

Recent figures show a reduction of pemphigus mortality from 90 per cent. before the use of steroids to a level of 33 per cent. after their use. Often very large doses are required. The response is best in pemphigus vulgaris: some cases remain clear whilst others require a maintenance dosage. Pemphigus foliaceus and pemphigus erythematosus respond less satisfactorily (Costello *et al.*, 1957). Severe icthyosis congenita has been successfully treated with cortisone at birth, with recovery of the skin to normal (Hanssler, 1957).

Chemical modifications which are said to minimize the risks of sodium retention and gastric disturbance are on trial as methyl prednisolone (Baer and Witten, 1958) and the hydroxy derivative of prednisolone (triamcinolone; 'adcortyl'; 'aristocort'; 'ledercort'). Early personal clinical impressions of the latter in several cases of exfoliative psoriasis, previously only semi-controlled with prednisone, are most favourable.

ACNE

Hormonal factors emerge as more important than all others in their influence on acne, especially in regard to the level of sex hormones whose effect depends upon the ratio, androgen + progesterone : œstrogen, and the sensitivity of the hair sebaceous follicles to the hormones. Experimental acne has been produced in women by administration of progesterone (Zeligman and Huebner, 1957). The influence of the pituitary appears in genito-pituitary relations and abnormal ovarian or adreno-cortical function. Three gonadotrophins derive from the anterior-pituitary: a follicle-stimulating hormone, a luteinizing hormone causing release of œstrogens in the female and androgen production in the male from the interstitial cells of the testes and thirdly a leucotrophin promoting secretion of progesterone from the corpora lutea. Serum gonadotrophin is under trial in acne, with reports of improvement (Baird, 1957). A recommended dosage is 'gonadyl', two tablets (each containing 50 international units) daily for the first month, one for the second and one on alternate days for the third; the tablets are allowed to dissolve under the tongue. Proper endocrine examination of patients is required to assess the factors concerned. For instance, it is suggested that acne with hyperœstrogenism (hypermenorrhœa, premenstrual tension) and normal or reduced pregnanediol may improve with small doses of œstrogens in the second half of the menstrual cycle, but with reduced œstrogens or progesterone, gonadotrophins may help (Peyri *et al.*, 1957).

Small doses of tetracycline hydrochloride will control secondary staphylococcal infection in papulo-pustular or cystic acne, although it has no effect on the comedones or acne process (Cronk *et al.*, 1956; King and Forbes, 1956). An initial dose of 250 mg. x 4 (1000 mg.) of tetracycline for four to seven days is reduced to a maintenance dose of 250 mg. or less daily and continued for weeks or months, apparently without ill-effect. Improvement

is said to occur in spite of no correlation between the antibiotic sensitivity and the results, although the lower enteric bacteria flora are altered (Loveman and Noojin, 1957).

MOUTH CONDITIONS

Recurrent or periodic muco-membranous ulceration of the mouth varies from minor or major forms of aphthæ to the larger often extensive necrosis of Behcet's syndrome with keratitis and vulvar ulcers, or more sporadically as in severe erythema multiforme (Stevens-Johnson syndrome), or persistently as pemphigus or pemphigoid bullæ. Mental stress is considered important in as many as 21 per cent. of the cases of aphthæ from which 1 in 5 people, predominantly women, are estimated to suffer (Sireus *et al.*, 1957). Some relief is claimed in these conditions by treatment with chlortetracycline, 250 mg. in 10 ml. of water as a mouthwash, or by hydrocortisone hemisuccinate sodium ('corlan'). Truelove and Owen (1958) record improvement in aphthæ with this. It is difficult accurately to assess results with a self-limiting condition such as erythema multiforme and results vary in this and pemphigus, some patients deriving increased comfort.

Black hairy tongue from antibiotic therapy or the chemical irritation of tobacco or mouthwashes is considered as a hypertrophy of papillæ with increased acidity inhibiting a keratinase enzyme and can be treated with 20 per cent. podophyllin in equal parts of acetone and alcohol as a keratolytic. Geographic tongue, assumed to be a benign type of pyogenic infection consequent upon excessive alkalinization, is amenable to treatment with chlortetracycline mouthwashes, to which 15 minims (1 ml.) of hydrochloric acid are added in cases of achlorhydria (Winer, 1958).

INFECTIONS

Monilia.—Monilia (*Candida albicans*) infection has increased due to the widespread use of antibiotics. After tetracycline treatment of pneumonia patients Childs (1956) found positive monilia cultures in sputum (38 per cent.), rectal swabs (26 per cent.), and throat swabs (24 per cent.). Nystatin, derived from the soil actinomycete, *Streptomyces noursei*, is lethal to monilia in a suspension of 100 units per ml. and harmless to the epidermis below 500 units per ml. (Funan, 1956), although contact dermatitis can occur. Preparations available include 500,000-unit oral tablets (adult dose 4 tablets in twenty-four hours), 5000 to 10,000 units in ointment, aqueous suspension or solution, and vaginal pessaries.

Nystatin seems unsatisfactory in systemic infections (Bereston, 1957), but is quite specific for superficial cutaneous and muco-membranous monilia, for which topical use alone is required. According to Grupper (1956), the following conditions respond to local use: perlèche, glossitis, stomatitis, ano-perineal and vulvo-vaginal infections, balano-posthitis, intertrigo, paronychia and nail infections. *Candida albicans* is also considered as a highly important infection in chronic paronychia (Whittle *et el.*, 1958).

Cross-infection from gloves occurs in gynæcological clinics, and thrush napkin eruptions are common; Bound (1956) reported that 3 per cent. of babies in an obstetric hospital were infected before six months, the mothers often having vaginal thrush.

Napkin eruptions.—In the ammoniacal Von Jacquet napkin eruptions, treatment with phenylmercuric nitrate, which inhibits the urease ammonia-producing enzyme from *Proteus vulgaris* (more important than *B. ammoniagenes* or *Ps. pyocyanea*), gives better results than the quaternary ammonium compounds (Brown and Wilson, 1957).

There is as yet only limited experience of the Japanese antibiotic, trichomycin, said to be effective against trichomonas and *Candida albicans* (Chappez and Bertrand, 1957).

Fungi.—The search for an effective antibiotic or chemotherapeutic agent against fungi, especially *Trichophyton rubrum* whose incidence is increasing, has been less successful. Nystatin is ineffective (Chakrabatz and Banerjie, 1957). Some success has attended early trials of glyceryl triacetate ('triacetin'): an esterase present in the skin, serum or fungi splits the compound to free acetic acid and glycerol. Improvement or cure is reported in tinea capitis (*M. audouini* more than *M. lanosum*), tinea cruris (*T. mentagrophytes, E. floccosum*), tinea pedis (*E. floccosum, T. mentagrophytes, T. purpureum*), tinea corporis (*T. purpureum, M. lanosum*) and tinea versicolor (Johnson and Tuura, 1956). Amide compounds on trial with favourable reports are substituted salicylamides, butyl phenamide (*N*-butyl 3-phenyl salicylamide) (Krafchuk and Beare, 1957), and 'nicetin' (22 dichloro-*N*-hydroxymethyl p-nitro phenacyl acetamide) (Brady and Gray, 1957).

Warts.—Cantharidin (dried blister beetle powder) has been introduced as a new treatment for warts (Epstein and Kligman, 1957): 0.7 per cent. cantharidin in equal parts of acetone and flexible collodion is painted on with a glass rod and covered with adhesive tape. It is of interest to note that blistering liquid B.P.C. 1949 (liquor epispasticus) contains 0.5 per cent. cantharidin, with castor oil and colophony, in acetone.

Gamma globulin.—Low amounts of serum gamma globulin (hypo- or a-gammaglobulinæmia) may be a congenital or an acquired condition (myelomatosis, chronic lymphatic leukæmia, lymphoma) (Firkin and Blackburn, 1958). The features are poor resistance to bacterial infections, a low titre of iso-agglutinins and an absence of circulating viral antibodies after immunization or actual infection. Ulcerating pyoderma gangrenosum with hypogammaglobulinæmia has been successfully treated with gamma globulin and steroid therapy (Bloom *et al.*, 1958). The duration of pityriasis rosea was halved (14.7 days compared with 31 days in an untreated control group) by convalescent pooled plasma but only if given in the first week, and considerably lessened (17.3 days) by pooled gamma globulin (Salem *et al.*, 1957). In herpes zoster, Epstein and Allington (1957) report that all the usual accepted treatments with antibiotics, vitamin B preparations, pituitary

extracts, corticosteroids and the like, including immune globulins, did not alter the course of this self-limiting disease.

LUPUS ERYTHEMATOSUS

Among some of the protean manifestations of lupus erythematosus are pyrexia, allergic conditions, drug sensitivity, urticaria, hay fever, general illness, loss of weight, functional nervous symptoms, arthritis, arthralgias, Raynaud's phenomenon, purpura and skin eruptions. Although borderline and transitional cases occur, treatment may still be considered under the two conventional groups of (a) chronic discoid, and (b) systemic lupus erythematosus.

Chronic discoid lupus erythematosus.—Mepacrine, which had compared favourably with the results of bismuth and gold, gave way to chloroquine, its main disadvantages being lichenoid dermatitis and yellow skin discoloration. Chloroquine also has its side-effects in dyspepsia, diarrhœa, pruritus, dermatitis, urticaria, nervous upsets, leucopenia, agranulocytosis, premature whitening of the hair and interference with the accommodation reflex of the eye (Goode, 1958). That blurring or misty vision may be due to whitish deposits in the cornea (Hobbs and Calnan, 1958) indicates the need for caution in the use of chloroquine. Hydroxychloroquine ('plaquenil') may be as good as chloroquine, though individual exceptions occur, and appears to be easily tolerated. It also has fewer side-effects, does not produce blood changes and enables a higher dosage to be given (Bennett and Rees, 1957). An initial dosage of 200 mg. is recommended, with fortnightly increases up to 2000 mg. The effect of antimalarials is suppressive, but not curative. Maintenance doses may be indicated for months or years, an 80 per cent. relapse rate one year after cessation of treatment being recorded (Rogers and Finn, 1956).

Systemic lupus erythematosus.—As natural remission occurs independently of treatment—38 per cent. being reported as improving spontaneously (Dubois, 1956)—evaluation of treatment is not easy. Conservative treatment at every stage until natural remission occurs is suggested (Hill, 1957), with rest in bed, salicylates for relief of pain, physiotherapy and removable plastic splints for arthritis, steroids being kept for the seriously ill or moribund patient. Mepacrine may be more effective than other antimalarials, especially in arthritis cases. Synergistic use of antimalarials enables the steroid dose to be reduced more quickly. Nitrogen mustard, originally recommended by Dubois (1956) for the more œdematous patients with renal lesions, improved a case in which such renal involvement precluded the use of corticosteroids (Davies, 1957).

Light-sensitive eruptions.—Chloroquine relieves some light-sensitive eruptions, not by any mechanical screening effect from tissue deposition, but by restoring the adaptability of the skin to ultra-violet light (Christiansen and Brodthagen, 1958). There is no effect upon the erythema response in normal people. Mepacrine, chloroquine and hydroxychloroquine give some

protection in cases of polymorphic light eruption (Bennett and Rees, 1957), solar dermatitis (Lamb *et al.*, 1957) and rosacea precipitated by sunlight. The non-specific, anti-inflammatory effect of chloroquine has led to its empirical use in creeping eruption from larva migrans (Burks and Kingery, 1956), acrodermatitis chronica atrophicans (Huff, 1955), panniculitis, and necrobiosis lipoidica. The need for care in the empirical use of antimalarials is emphasized by reports of exfoliative dermatitis in psoriasis (Cornbleet, 1956) and rheumatoid arthritis (Granirer, 1958) treated with chloroquine.

BRITTLE NAILS

Brittle nails seem unrelated to calcium or phosphorus metabolism or to thyroid function. The cause is still unknown although occupational factors play some part. Improvement occurred in 43 of 50 patients given 7 grammes of gelatin a day for three months (Rosenberg *et al.*, 1957). Gelatin contains 26 per cent. of aminoacetic acid (glycine) which may be the active ingredient.

INDUSTRIAL DERMATOLOGY

Attempts have been made to neutralize or inactivate sensitizing chemicals important in industry, and these may indicate future trends. The effect of turpentine, whose irritative action increases with time, and the oxidation of terpenes to peroxides (Pirila and Siltanen, 1956) are inhibited by agents preventing oxidation such as 1 per cent. sodium bisulphite, or 1 per cent. triethanolamine (Rajka *et al.*, 1955). Vitamin C, a reducing agent, protects against chromium. Hexavalent chromium (not trivalent or metallic chromium) sensitization is important in lithography, printing, tanning and leather trades, paintworks (zinc chromate primers), electroplating and cement works, and 5 per cent. sodium bisulphite has been recommended for hand-cleaning in such trades as it reduces the hexavalent to trivalent chromium. Cole (1953) records improvement in chronic chrome dermatitis with an ointment containing 3 per cent. dimercaprol. Chelating agents form stable complexes with metals and have been used as ethylenediamine tetra-acetic acid or its calcium salt for lead poisoning: 10 per cent. of the former or its calcium salt will inhibit a positive patch-test with nickel and is said to protect against nickel-suspender dermatitis. Although unsuccessful against chromium in experimental patch tests, possibly because it chelates trivalent and not hexavalent chromium (Samitz, 1956), 10 per cent. 'calcium disodium "versenate"' in hydrous wool-fat ointment is reported as successful in chrome ulcers (Maloof, 1955).

BARRIER CREAMS AND PROTECTION

At the present moment barrier creams are either water-soluble or water-repellent; the incorporation of chelating or neutralizing agents into detoxifying barrier creams may be for the future. Incorporation of polymeric phosphates, which impede the fixation of heavy metals, and fat-soluble dyes in the skin is suggested (von Czetsch-Lindenwald, 1957). Water-repellent silicone barrier creams find non-industrial uses in protection of the skin around a colostomy, ileostomy, tracheotomy, or other fistulæ, and for

bedsores. They prevent soiling or maceration from incontinence or chronic nasal discharge, and protect the skin around leg ulcers or in perianal eczema and pruritus ani before defæcation (Odengaard, 1957). They also have a use in napkin eruptions and intertrigo and as a nocturnal application in cases of perlèche and lip fissures so often associated with ill-fitting and loose dentures. Synthetic resins such as meta-acrylic-acid esters ('nobecutane') have possibilities in industrial use, either as lacquers or as transparent sterile and washable wound-dressings, and may be sprayed on to provide protection from oils, chemicals, detergents, glass or metal particles (Weber, 1957).

RADIATION

Anxiety, both national and international, on the amount of irradiation to which the populace is now exposed indicates the need to reduce unnecessary radiation. This has taken the form of more reliable dose-meters, using soft rays from beryllium-window x-ray tubes, with punch biopsy measurement of the exact depth of the tumour (Polano, 1958); ultra-sound treatment combined with chaoul contact irradiation, for which 40 per cent. reduction is claimed (*Derm. Wschr.*, 1956), Grenz rays with less black scatter, and radioactive isotopes. Such isotopes, natural or artificially made, are in use as thorium-x (mostly alpha rays), phosphorus, arsenic, strontium emitting β rays and, probably most important of all, cobalt which approaches radium in its beta and gamma radiation (Witten, 1956). Isotopes can be applied in needles, in tubes, by injection, by external applicators of various shapes, or by actual intra-tumour injection (Czerniak and Zuprkowski, 1957). Disappearance of mycosis fungoides infiltrates following total irradiation of the skin with high-speed electrons is reported by Edgecomb *et al.* (1957). Twiston Davies (1956), however, casts doubt on the efficacy of conventional doses of x-ray in eczema and, after comparison of symmetrical areas of treated and untreated lesions, concludes that anticipation of the dose is as effective as the dose itself!

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ADVANCES IN TREATMENT OF DISEASES OF THE EAR, NOSE AND THROAT

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Scientific advance is rarely a steady progress but is rather a cycle of sudden spurts alternating with periods of consolidation, in which mature consideration, selection and experiment pave the way for the next forward step. The periodic forward surges of scientific knowledge are stimulated by different agencies. It may be that the invention of some new apparatus or the adaptation of some scientific principle makes possible techniques which previously were outside the surgeon's grasp, or it may be that the discovery of a whole series of new drugs or agents of hitherto unsuspected potency solves problems and gives comfort and safety to patient and surgeon alike. In many instances such discoveries may be combined so that one is complementary to the other.

Chief among these agents have been the sulphonamides and the antibiotics. These have reduced the surgery of sepsis to such a degree that it has been fashionable in some quarters to say that nose, throat and ear work is a vanishing specialty. Nothing could be further from the truth, for, whilst sepsis has all but disappeared, the time consumed previously in its treatment is now employed to infinitely better purpose in the preservation and restoration of function. This is real progress and in the right direction.

Following on the security provided by antibiotics, the use, now almost universal, of the operating microscope opens up new fields for surgical investigation of problems of physiological function which are limitless. Anæsthesia has rendered surgical treatment in every area safer and simpler, and the use of induced hypotension has improved results and enabled the operating microscope to be used to the greatest benefit. The bloodless fields obtained have greatly increased the safety and accuracy of many operations.

There are advances in other spheres, particularly in radiation of various kinds, and in drugs, notably hormones, which have all contributed to progress.

THE NOSE

In nasal disease advance has been in some ways less spectacular than elsewhere, but has been none the less real. One of the factors contributing to this progress has been a better and fuller understanding of the physiology of the nasal mucous membrane, with the result that surgical insults to the nasal structures are perpetrated far less often than in the past.

Conservatism.—It is realized that one of the chief functions of the nose is

humidification and warming of the inspired air. This is combined with other functions such as cleansing and filtration. The erectile tissue in the nose reacts according to atmospheric conditions to provide the correct conditions for comfort. When there is any variation from the normal, either from outside irritations such as dust or infection, or from within by vasomotor instability, comfort disappears and nasal symptoms make their appearance. These symptoms may be excess of secretions or change in their consistency, and failure to realize the background to such conditions has led in the past to much unnecessary nasal operating. Conservatism here constitutes progress, for it is realized more clearly that once the ciliated mucous membrane has been severely traumatized there can be no return to normality and complete comfort.

Oils and sprays.—All treatment therefore, whether drug or surgical, is directed towards preserving and restoring the function of the nasal mucous membrane. Any drug or preparation which slows down or causes eventual cessation of ciliary action is harmful. This applies to all salves or powders or oils which clog up the ciliary mucous membrane and also to those drugs which are helpful at first as decongestants, but which on repeated use lose effect and lead to the patient being in a state where no treatment is of any avail. Ephedrine solution in some form or other, up to 2 per cent. solution, remains the sheet anchor and the active principle of many proprietary preparations.

Antihistamines.—There have been great advances in the treatment of vasomotor conditions of the nose by drugs. Foremost among these are the antihistamines. They are valuable in specific forms of vasomotor rhinorrhœa such as hay fever and other allergic conditions, and also the non-specific types such as sensitivity to temperature change, climatic conditions and the like. In general, the younger the patient the more effective are the antihistamines. This is particularly so in the type of child who suffers from constant and repeated colds. In many instances these are a manifestation of some form of imbalance leading to rhinorrhœa, and may be traced to such varied causes as 'school' milk, the fumes from the bus on the way home, or the family cat or dog. A good combination of these drugs is phenindamine and promethazine given in appropriate dosage.

Cortisone.—A more far-reaching treatment in somewhat similar circumstances is the use of cortisone. This is a drug which must obviously be used with caution and with proper controls, but there is no doubt that some allergic diseases respond dramatically to its use. Used in moderate dosage many cases of rhinorrhœa benefit greatly from it. As in similar circumstances elsewhere withdrawal of the drugs heralds relapse, but it is possible to stabilize dosage in many cases at such a low level that no serious consequences need be feared. Cortisone should be given by mouth. Local treatment has been the subject of experiment but in general is less effective as it is difficult to achieve sufficient concentration for a sufficiently long time if copious nasal secretion is present.

Some of the newer and more powerful preparations may give greater improvement but more experience is required before this can be clearly established.

SINUSITIS

The treatment of sinusitis has undergone no dramatic change. In acute infections rest and the use of decongestants are still standard treatment, but antibiotics have been used widely. It is as well to recognize clearly what antibiotics can and cannot do in sinusitis. In the adult it has been shown conclusively that antibiotics do not penetrate into the maxillary antrum in bacteriostatic levels. Clearly therefore they cannot be regarded as curative of the sinusitis though generalized infection will be controlled in the usual way. It must be appreciated, however, that the removal of general symptoms and the introduction of a sense of well-being before the localized infection has been eliminated may in some cases be productive of chronic infection. When this is suspected apparent recovery should be checked by 'follow-up' x-rays. After infection x-rays are often unreliable as the changes induced by infection may remain even though the infection has been eliminated.

To exclude any possible error a small quantity of radio-opaque oil is introduced into the maxillary antrum by needle and syringe; x-rays taken thereafter will show clearly any chronic thickening of the mucous membrane. Further information can be obtained, for Proetz has shown that mucous membrane functioning normally will completely clear the antrum of a radio-opaque oil within three days. The emptying time, from study of the 'three day' film, can be ascertained.

Antibiotics.—Antibiotics are sometimes introduced directly into the sinuses, by the insertion of polythene tubes through a trocar, or injection of a preparation which will be effective over a period of days, such as an oily solution of procaine penicillin.

PHARYNX AND LARYNX

The *tonsils and adenoids* problem is of continuing interest, but at present the only 'live' issue is the relationship between tonsillectomy and poliomyelitis. Statistics are confused and confusing and by no means convincing, but it seems to be generally agreed that, if infected, tonsillectomy renders the patient more susceptible to bulbar forms of the disease. How far therefore tonsillectomy should be carried out during the season when poliomyelitis may be encountered is a problem for the individual concerned. It is usual here to refuse to perform the operation on any patients from an area in which there is known to be an outbreak but otherwise to make no difference between the seasons. The influence of vaccination for poliomyelitis upon operation has been the subject of discussion and six weeks should be allowed between vaccination and operation. It is probable that this is a substantial error in the right direction.

Tracheostomy.—The recognition of the value of tracheostomy in the treatment of poliomyelitis in ensuring early lung drainage is a very real

improvement in treatment. It has given impetus to the development of new techniques to combat the effects of pharyngeal and laryngeal paralysis.

Radiotherapy.—In the treatment of malignant disease of the pharynx and larynx, radiotherapy has made considerable progress, chiefly owing to the development of very high voltage apparatus, so that accuracy of dosage and certainty of application have been greatly improved. Indeed, in some centres success in this treatment has been so marked that primary surgery in cancer of the larynx is rarely practised. Surgery in such circumstances is reserved for the failures of radiotherapy and, although figures of final recovery may not do more than equal those of primary surgery, the number of patients who continue to enjoy the function of natural voice is much greater.

THE EAR

It is in the treatment of diseases of the ear that advances have been most spectacular. Antibiotics have rendered possible operations which formerly carried serious threat to life, and the operating microscope, under which work is carried out at ten magnifications or more, has caused surgeons everywhere to work to standards of accuracy and precision which were undreamed of a few years ago. This is due to the experience gained in the fenestration operation, for interest was aroused not merely in finer techniques but in the fundamental problems of restoration of hearing function.

Reconstruction.—The modern otologist is not content to eliminate disease in the ear, but he sets out to reconstruct the middle-ear mechanism so that resumption of physiological function is possible. This is done by tympanoplastic techniques in which perforations of the drum membrane are closed; even when a drum membrane has been completely destroyed it is often possible to reconstruct it by skin grafting so that hearing is greatly improved.

For a very long time it has been known how to close small or even moderate-sized perforations of the drum membrane, and thereby restore lost hearing to a large degree. This was done by removing the ingrowing epithelium from the edges of the perforation either by scraping it off or touching it with acid. This stimulated the tissues of the drum membrane to heal and was very successful in suitable cases. The very large or subtotal perforation, however, was a problem which was insoluble, until, within the last few years, new techniques were devised which enabled larger skin grafts to be employed successfully. This is known as 'myringoplasty' and is suitable only in such cases as have been completely healed and dry for many months. The advantages of this repair, particularly in the young, are obvious. Whether or not the restoration of hearing is accomplished the social rehabilitation of the child is extremely important and such activities as swimming, previously forbidden, are made possible by this operation.

In the majority of cases, however, more extensive operation is required as quiescent disease may be present in other parts of the middle-ear cleft. This is known now as a modified radical mastoid operation with tympanoplasty. In these procedures the structures of the middle ear are closely

examined under the microscope and all disease eliminated. An attempt is then made to reconstruct the middle-ear mechanism and to graft the middle ear so that the drum membrane is reconstructed as a functioning structure. The principles governing the working of the middle-ear structures under the conditions of disease are imperfectly understood and much experience is required before these techniques will be standardized. Meantime they must be regarded to some extent as experimental. All grades and types of operation may be demanded and it is often impossible to predict the extent of the operation required before the petrous bone has been opened and the middle ear and the mastoid antrum inspected.

In non-suppurative deafness there have also been great advances. Most people are now familiar with the fenestration operation which has passed into the category of standard surgical procedures. This is carried out for the relief of deafness due primarily to otosclerosis, and it now carries a high probability of successful treatment. It is unnecessary to enlarge here upon this treatment, but another technique has been devised which is in a sense a corollary to the fenestration operation. This is known as 'mobilization of the stapes' and it constitutes a very real advance in treatment.

Mobilization.—Deafness in otosclerosis is due to the immobilization of the stapes in the oval window by the overgrowth of the otosclerotic bone process, so that movement of the ossicular chain is not communicated to the cochlea or hearing organ in the usual way. In the new technique the surgeon sets out to break down the adhesions and the bone, which are fixing the stapes, by means of forcible movement of the stapes. Access is obtained by folding the drum membrane forwards so that the stapes and the medial wall of the middle ear are open to plain view and inspection under the microscope. The stapes can then be grasped under vision and moved in such a way that in some cases complete mobility is regained.

As compared with the fenestration operation this is a simple procedure. It is done under local anæsthesia and does not require any external incision. The operating time is short and recovery is rapid as the stay in hospital rarely exceeds two days, and there is no after-treatment. It would seem that this could replace the fenestration operation, but this is not by any means the case, for it is complementary to the more formidable operation. The simplicity is offset by a low success rate. Fifty per cent. success is a fair average, and probably a lower figure will turn out to be more accurate, whereas the fenestration offers a success rate of between eighty and ninety per cent. The two operations must therefore be regarded as stages in the treatment of this form of deafness, treatment which should start with the mobilization operation and conclude when necessary with the fenestration. The otologist who undertakes this treatment should be equally skilled in both operations.

MÉNIÈRE'S DISEASE

Deafness with vertigo is often labelled Ménière's disease and is a most crippling condition.

Diet and drugs.—Treatment of Ménière's disease is now to a great extent standardized, and a routine, both dietary and drug, is followed, which gives a fair proportion of cures or at least control. The standard treatment is to limit fluid and salt intake and administer at the same time small doses of barbiturate: e.g. phenobarbitone, 1 grain (60 mg.) at night. At the same time the patient is given nicotinic acid by mouth in moderate cases but by injection in severer affections. By mouth, 50 milligrams twice or, if tolerated, thrice daily is an average dose, and this must be persisted in for several weeks. In case of failure a change is sometimes made to histamine which is given by injection in gradually increasing dosage. Another similar drug which may be used is riboflavine. These drugs have a similar action and if there is any element of migraine, as there sometimes is, a change to ergotamine tartrate may give great improvement. More recently, antihistamines have become popular, probably through their use as anti-seasick remedies, and in some cases of Ménière's disease they appear to help. At present, however, they take second place to nicotinic acid and similar drugs.

The chief difficulty in judging the effects of treatment is the natural tendency to remission in the course of the disease. Remissions are unpredictable and vary in duration from weeks to years. When, therefore, a course of treatment is given and the attacks cease, the tendency is to ascribe the improvement to the treatment but this is not always justifiable. On a long-term assessment of the effects of these treatments it is evident that considerable benefit is gained and cure is effected in many cases, but there are always the few cases which fail to respond to treatment and yet are severely handicapped. These cases separate themselves in two groups: (i) a group in which the hearing is so poor as to have ceased to be of any value; (ii) a group in which hearing remains reasonably good.

Labyrinthectomy.—Treatment of the first group is simple and speedy. The labyrinth is put out of action by surgical means and the symptoms immediately disappear. There may be a period of rehabilitation, particularly in the case of elderly people, but complete recovery is the rule.

Sympathectomy.—The difficult group is that in which the hearing is worth preserving. No surgeon is willing to destroy hearing, and when it is known that a percentage—happily small—of patients develop bilateral disease, the problem is to find a treatment which will render the disease inactive but at the same time preserve hearing. This problem has been the subject of research for at least twenty years, but until recently the solution has eluded otologists. Sympathectomy of the cervical or cervico-dorsal part of the chain seemed to give some promise, but has not become popular.

Ultrasonics.—More recently, ultrasonic radiation has been applied to the labyrinth with considerable success. By a comparatively simple approach operation the balance part of the labyrinth can be put out of action while the cochlea remains intact. Further experience in this method is required before it can be universally recommended but it constitutes a considerable advance on other methods of treatment.

ADVANCES IN OPHTHALMOLOGY

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Over four thousand articles are written annually upon ophthalmological subjects, and this enormous output makes the task of keeping abreast with recent advances excessively difficult. The preparation of a short survey has its own particular problems of selection and presentation, but the proceedings and transactions of the various medical societies form a useful basis from which to survey the advancing borders of knowledge.

PROBLEMS OF LACRIMAL OBSTRUCTION

The control of acute infections and the general improvement in social conditions have led to a reduction in the number of acute infections of the tear passages. Watering of one eye in babies responds to simple pressure in the large majority of cases; a few require to have a probe passed once, or to be syringed. A distressing and difficult traumatic group arise from motor accidents. If the canaliculus is cut reconstruction should be carried out with minimal delay. One method is to insert a fine nylon thread through the upper punctum by means of a curved lacrimal needle; by passing this through the lower punctum accurate apposition of the torn ends may be achieved. The thread is left *in situ* for ten days. Stenosis of the tear ducts arising from radiation treatment of rodent ulcers can present difficult problems and the results of operation may be unsatisfactory. For the large group of elderly people with chronic obstruction of the lower end of the tear sac the operation of choice is some form of dacryocystorhinostomy: that is, a passage from the tear sac opening into the middle meatus of the nose. Operations of this type have largely replaced simple excision of the tear sac, which is now outmoded.

RHEUMATISM AND UVEITIS

In a large survey carried out in Manchester it was found that, on the whole, rheumatoid arthritis as generally understood was not associated with uveitis. In Reiter's disease it is probable that uveitis is in fact a part of the disease syndrome. Spinal arthritis was often associated with an anterior uveitis and this may be the initial symptom in ankylosing spondylitis. An appreciable number of patients with typical rheumatoid arthritis were found to have dry eyes, and it is believed that there may be an excessive number of patients with keratitis sicca who also suffer from rheumatoid arthritis.

HERPETIC INFECTIONS OF THE OUTER EYE

Herpes simplex arises from a widely spread virus and is most commonly seen in the form of small vesicles around the mouth and nose. When the eye is affected a dendritic ulcer of the cornea may arise. This is best treated in the early stages by local destruction of the epithelium by the use of carbolic

or absolute alcohol. Disciform keratitis may be of herpetic origin, but both these conditions are unconnected with the virus of herpes zoster. In herpes simplex recurrences are common; the reason for this is not clearly known. It is of importance to know that cortisone is of no value in these conditions, and may be harmful. Radiotherapy may be of great help in the treatment of herpes simplex affecting the cornea. It may be employed in the form of beta-radiation (500r weekly for four weeks) or low-voltage x-rays. This treatment may eradicate unwanted blood vessels, reduce granulation tissue and promote epithelial healing. It is also of value in relieving pain.

Herpes zoster is found over the distribution of the ophthalmic division of the fifth nerve and there is an association between the virus of zoster and that of chickenpox. As in the simplex condition the prevention of secondary infection is of the greatest importance. Modern therapeutic agents can control this danger to a greater extent than in former days, but there is no specific treatment. The cornea, iris and ciliary body may be involved and the onset may be delayed. Intractable neuralgia is a residual complication which may give rise to much suffering. Cases are on record in which a leucotomy was necessary before the condition could be relieved.

RADIOACTIVE PHOSPHORUS AS A DIAGNOSTIC AID

Intra-ocular neoplasms may be diagnosed clinically with considerable confidence, but difficulties arise from time to time. In such cases radioactive phosphorus, P^{32}, may provide supplementary evidence. Malignant melanomas concentrate P^{32} to a greater extent than other ocular tissues. This concentration does not occur in serous detachments, vitreous hæmorrhages or degenerative lesion of the retina and choroid; nor does it occur in retinoblastomas. To be regarded as positive there must be a 30 per cent. difference in concentration between the affected eye and the normal fellow eye. In patients with one eye differential readings may be made between the quadrants. Readings are taken between twenty-four and forty-eight hours after the injection of the material. Radioactive iodine has proved unsatisfactory as a diagnostic aid.

TONOGRAPHY

Tonography has been defined as a method for the measurement of the facility of aqueous outflow in the intact living eye. The measurements are read from the scale of an electronic tonometer of the Schiötz type which is held in position upon the cornea for four minutes. The weight of the instrument squeezes aqueous out of the eye and this depends upon the efficiency of the drainage area at the angle of the anterior chamber. In closed-angle glaucoma the aqueous outflow shows impairment particularly in the congestive phase or where there are peripheral synechiæ. In such cases the outflow returns to normal when the angle is opened up. These facts are already known. In chronic simple glaucoma where the angle appears to be open the test may show a permanent resistance to outflow. This is the most important finding that has been made in tonography. It is believed that the abnormal

resistance to outflow is the basic observation of importance and that the findings are not due to hyperformation of aqueous. The instrument, however, is still of more value for research purposes than for routine clinical use.

VASCULAR CHANGES AND VISUAL FAILURE

It is better to talk of the malignant phase in hypertension and thus avoid the impression that malignant hypertension is in some way a different disease entity, which it is not. It is in the malignant phase that gross retinal changes occur and, in particular, when the diastolic pressure is in excess of 140 mm. Hg. If by active treatment the diastolic level can be maintained around 100 to 120 mm. Hg retinal changes may be prevented and even reversed.

During recent years a variety of forms of defective vision have been identified as arising from obstruction of one or more of the main arteries in the neck. A particularly interesting condition occurs with bilateral infarction of the occipital lobes. These cases are relatively rare and may be of more interest to the specialist than to the general practitioner, but the possibility should be kept in mind in cases of obscure blindness, particularly of one eye. The effects of such occlusive arterial lesions at regional and local levels depends upon the available collateral blood supply. The colour and other visual illusions found in the elderly are associated with temporal-lobe arteriosclerosis. There is little doubt that many of these obscure conditions are being seen more commonly as a result of the changing age structure of the population. This forms yet another facet of the rapidly changing pattern of day-to-day clinical work.

RETINAL VENOUS THROMBOSIS

Accounts are appearing in the clinical literature which support the view that anticoagulant therapy may be of real help in the treatment of this condition. It is particularly suitable in branch thrombosis and not so satisfactory in central venous blocks. The most favoured substance is phenindione. The reported successes have been in patients admitted to hospital and this factor in itself makes assessment difficult. Indeed, it is probable that many of these patients do, in fact, improve as a result of the regimen rather than of the therapy employed.

LIGHT COAGULATION AND DETACHMENT OF THE RETINA

About twelve years ago Meyer-Schwickerbath, in Germany, had under his care some patients who had suffered from burns of the retina after looking at an eclipse of the sun. Upon this basic clinical observation he developed the technique of light coagulation of the retina in cases of detachment of the retina. In the first instance sunlight was used, but later, after much experimental work upon rabbits, a special arc lamp was developed for the purpose. The main problems were in relation to the intensity, duration and wavelength of the light. These matters have now been solved, but the apparatus is still very expensive. It is, in fact, a method of producing choroido-retinal coagulation and, as such, does not differ in its objective from other well-

established methods such as diathermy. The particular merit of light coagulation is the fact that it can be carried out under visual control. The operator looks at the retina through the optical system in a subdued light and directs the focusing system to the desired point. An exposure time of one second is sufficient to cause the spot to coagulate. This procedure is particularly suitable for shallow detachments, either at the central area of the retina where access by standard means is difficult, or for suspicious areas at the periphery where, in suitably selected cases, a prophylactic coagulation may be carried out. The retina itself is not a light-absorbing tissue and, consequently, it is the layers behind the retina that are most affected; it follows that the retina and choroid must be near each other to achieve satisfactory union by this method.

It may also be used in the treatment of very small retinoblastomas and in melanomas of the choroid. Very good results have been obtained in the treatment of angiomatosis of the retina when a small area can be coagulated at a time. This procedure seems to be a definite advance upon the older treatment of these intractable conditions.

PLEOPTICS

For over half a century the basic objectives in the non-operative treatment of squint have been the correction of refractive errors, occlusion to overcome amblyopia, avoidance of suppression, control of false projection and the attempt to develop binocular vision. The amount of surgical treatment which is required is an indication of our failure to develop effective procedures under these various headings. Amblyopia means blunt vision and it is said to be present in 15 per thousand of the population. The defect has a sensory and a psychological component and more attention has been paid to the former than to the latter. The word pleoptics was introduced by Bangerter as a comprehensive term to include all forms of treatment of the amblyopic eye. Over a hundred sessions may be required in the treatment of one case and involve the coordination of hand, ear, and memory.

Several ingenious instruments have been designed to discourage the use of a false macula by dazzling the area prior to binocular exercises. A form of ophthalmoscope has been made by Cüppers which projects a black star upon the retina. By this means it becomes possible to measure the distance from the point of fixation and the macula with great accuracy. By such methods patients can be classified into groups and it appears that a certain number may derive great benefit from this intensive treatment. Great perseverance and persistence may be required as treatment may need to be carried out twice or three times a day for several months.

This revival of interest in the intensive development of retinal function inevitably recalls the remarks of Javal who published his observations in 1896 after a lifetime of study. He wrote:—

'The first time that I explained to von Græfe my methods of treatment, this confrere, equally well known for his good nature as for his professional attainment,

stupefied me by saying to me that people were not worthy of such pains. The experience of life has led me to recognize that von Græfe was right. One has seen that to conduct to a successful issue certain cures, time and patience out of all reasonable proportion is necessary'.

This may be the case in the present interest in development of retinal function if the treatment is going to interfere to a serious extent with the educational growth of an otherwise healthy child.

VISUAL AIDS FOR THE PATHOLOGICAL EYE

Visual aids for the pathological eye, excluding the use of contact lenses, were the subject of a general discussion at the Oxford Ophthalmological Congress in 1956. In various parts of the country visual aid clinics have been established where patients may be advised and fitted with appropriate optical devices. The problem can be considered in three well-defined groups. There is the schoolchild suffering from partial sight for whom special provisions have been made for over fifty years; there is the tragic, but relatively small, group of adults developing defective vision in the course of a working lifetime, and there is the much larger and increasing category of elderly blind people who develop degenerative changes within the eye.

The schoolchild can be helped materially if proper equipment is available. There is a shortage of educational books printed in 14 or 18 point type. To make good this deficiency would be both costly and bulky. Most of *The Practitioner* is printed in 11 point type, and the smallest newspaper type in common use is 5 point. It can be readily seen that books printed in type such as is used at the head of this page might present practical difficulties. One method of overcoming the problem is by the use of epidiascopes and projectors which give some degree of magnification, but lateral distortions may occur. Film strips are a more satisfactory method, and they are being used to a greater extent every year. As in the case of large-sized type in the printing of books, the cost is rather great, particularly as the probable number of copies required is small. The use of ciné projectors has not been very successful in the education of the partially sighted child.

Typewriters are of great value in the education of those with defective central vision. I have had under my care several children who have achieved considerable academic distinctions when they were permitted to sit for examinations with ordinary typewriters. For the earlier education of the partially sighted, typewriters with large type may be used; as these are in commercial production the cost factor is not so great as in the printing of special books. The various duplicators now being advertised are making a further contribution to the solution of this problem.

The fundamental base for all forms of help, by optical means, to the partially sighted is the Galilean telescope. This can be constructed quite easily from a standard trial case by using a minus-twenty lens as an eyepiece and a plus-ten lens as an objective. This gives a magnification of about 2× which is sufficient for use in a theatre or opera. I often use such a glass for testing patients with defective central vision because if they see better with

the instrument then they stand a very good chance of benefiting by the use of various visual aids which are now in commercial production. If there is no appreciable benefit with a simple opera glass, which is constructed upon Galilean principles, then a visual aid may not be a help. Prismatic glasses do not necessarily make a larger retinal image and so do not constitute such a simple screening test.

All attempts to help the visually handicapped depend upon four basic principles: magnification, lighting, field of vision, and definition. High magnification may lead to a serious reduction in the field of view and it becomes very tedious if only a word or two can be seen at a time in place of the grouped reading of the normal adult. Similarly, a loss of definition and brightness does not compensate for a reduction in visual field. Trial and error still play a part in the employment of visual aids, but much good work has been done by British firms of dispensing opticians in attempts to overcome this hit-or-miss approach.

The visual acuity falls away rapidly from the central line of vision and binocular vision may prove to be impracticable. Many of these patients prefer monocular vision when using a magnifying glass or other device and, in my view, this is quite harmless and they should not be discouraged from doing so. Lighting is important and the present standard for school lighting is 10 lumens per square foot; this can be doubled for partially sighted patients with great advantage. Many young people are very self-conscious of their handicap and are unwilling to go about wearing telescopic spectacles: it is a common sight at a theatre to see young women removing their myopic correction at the end of the act preparatory to having their tea and biscuits.

Elderly patients present a specially difficult problem. Many, of course, have never done much reading at any time in their lives, but the middle-class intellectual can be a very difficult patient. Simple devices such as a black reading-screen with a narrow horizontal slit may enable many such people to read with less discomfort, by cutting out collateral illumination. From time to time articles appear in the lay press describing some spectacular device which will improve failing vision. They all depend upon the four basic principles mentioned already, and the claims must be accepted with great care. It is cruel to raise the hopes of the visually handicapped by specious advertising.

This article is based upon original articles and discussions presented during the past three years to various ophthalmological societies in Britain and published in the *Transactions of the Ophthalmological Society of the United Kingdom*. Detailed references to the various authorities are not given, but will be found in the volumes from which the abstracts have been made. In assembling the material consideration has been taken of the ophthalmological topics which have been the subject of recent articles in this journal in order to avoid repetition, although some degree of overlapping is inevitable.

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ADVANCES IN THE TREATMENT OF DISEASES OF THE BLOOD

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THE past two or three years have seen relatively few noteworthy therapeutic developments in hæmatology, in contrast to the preceding decade which was a period remarkable for its productivity. This comparatively fallow period, however, has provided a useful breathing space for the continued clinical assessment of many of the newer therapeutic agents, which consequently can now be evaluated with more confidence than was possible only a few years ago. In this article an attempt will be made to survey briefly those of the newer advances which seem to merit an established place in contemporary therapeutics.

IRON-DEFICIENCY ANÆMIAS

Inorganic iron salts given by mouth continue to provide the treatment of choice for the great majority of patients. Genuine intolerance to oral iron is rare: in most cases in which it is alleged to occur it can be overcome by working up to the optimal dosage gradually, ensuring that the drug is taken after meals, and by encouraging the patient. Of the many preparations of medicinal iron for oral use, ferrous sulphate deservedly remains the most popular. It is more convenient than liquid preparations, and, in view of dispensing fees, cheaper even than ferric ammonium citrate. For the various more expensive preparations it has been claimed that they are more effective and more readily tolerated. There is no convincing evidence that they are more effective, and it is only infrequently that a patient is encountered in whom they do appear to be better tolerated than ferrous sulphate, when this is given a fair trial. The liquid preparations are of value mainly in patients having difficulty in swallowing pills, as for example in the Plummer-Vinson syndrome. On theoretical grounds they might also be preferred in patients with peptic ulcer, although in practice trouble is seldom experienced with pills in such patients.

There is evidence that ascorbic acid facilitates the absorption of iron and this should therefore be given if there are reasons for suspecting a concomitant deficiency in this vitamin. In the absence of such a deficiency, however, it is improbable that the vitamin is of therapeutic value.

The parenteral administration of iron has now become an established procedure. At first the intravenous route was the only feasible one, but more recently an iron dextran preparation, marketed under the name of

'imferon', has become available for intramuscular injection. On the grounds of convenience and reduced liability to undesirable side-effects the intramuscular is superior to the intravenous route. Even with this, however, unfavourable reactions such as pyrexia, and pain at the site of injection, occasionally occur; and staining of the skin is not uncommon. To avoid this the injection should be made as deeply as possible into the muscle, and be followed by light massage. Treatment should be started with a small dose, such as 25 mg. of iron in 1 ml. of solution, and then increased to 100 mg. daily. The total dosage may be calculated on the basis of 25 mg. of iron being needed to restore the hæmoglobin level by 1 per cent. Care should be taken not to overdose, since excess of iron accumulates in the tissues and may possibly lead to damage of the liver and other organs.

Parenteral iron is not necessarily more effective than iron given orally, since either method may result in a daily rise in the hæmoglobin of 1 per cent. or more. It should therefore be used only when there are definite indications. In general, its use should be confined to patients falling into one or other of the following categories. (1) Genuine intolerance to iron by mouth, and, as already mentioned, this is rare. (2) Anæmia due to recent gastro-intestinal hæmorrhage, when oral therapy might be injudicious. (3) Anæmia due to alimentary malabsorption, as in steatorrhœa. Oral iron is often effective in these cases, but sometimes it is less effective than parenteral iron. (4) Anæmia in the later stages of pregnancy, when it is desirable to restore depleted iron reserves with as much speed and certainty as possible. (5) Finally, perhaps the largest group, there is the unreliable patient who cannot be depended upon, as an outpatient, to take iron regularly by mouth. In this connexion it is a common experience of the hospital physician to admit a patient suffering from iron-deficiency anæmia who is said to be refractory to oral iron therapy, but under hospital discipline makes a rapid recovery in response to oral iron in the usual dosage.

MEGALOBLASTIC ANÆMIAS

Addisonian pernicious anæmia.—Vitamin B_{12} (cyanocobalamin) given parenterally is now the treatment of choice, and deserves to supplant liver extracts completely. It is entirely reliable, it can be given conveniently and cheaply in doses considerably exceeding those contained in practicable quantities of liver extract, and is almost free from risk of sensitization.

For the initial treatment of pernicious anæmia it is as well to give cyanocobalamin in generous doses, since there is widespread tissue deficiency of the vitamin. There is no evidence that high dosage is ever harmful. Accordingly, it is sound practice to administer 1000 micrograms of cyanocobalamin intramuscularly as soon as the diagnosis is firmly established. This amount is available in an ampoule of one millilitre. It is of interest to note that to give the same dose in the form of a natural liver extract, even in one of the highest potency, about 100 ml. would be necessary. After the

initial loading dose, a weekly injection of 100 micrograms is usually adequate for the restoration of a normal blood picture at optimal speed. In patients with neurological complications, or in those whose response may be hampered by infective or degenerative conditions, the injections should be given twice weekly.

Once a normal blood picture has been achieved, it can usually be maintained by an injection of 100 micrograms of cyanocobalamin once a month. Since patients vary in their requirements, if this dosage is found inadequate it should be given more frequently. In the presence of neurological complications, it is advisable to give 100 micrograms once a week so long as there is any evidence of continued clinical improvement. In an attempt to reduce the frequency of injections in the maintenance treatment of uncomplicated cases, observations have been made in my clinic on the effect of giving 1000 micrograms at three-monthly intervals. The results, however, have not been altogether satisfactory since in a small proportion of the patients the blood counts and the serum vitamin B_{12} levels have shown a tendency to fall. It is therefore recommended that in routine practice injections should be given at intervals not exceeding a month.

To overcome the need for injections, preparations suitable for oral administration have been produced containing cyanocobalamin together with intrinsic factor, usually obtained from hog's duodenal mucosa. Experience in a number of centres with this form of treatment has shown that, although good initial responses occur in the majority of patients, the long-term results are unsatisfactory in an unacceptably high proportion of patients. Furthermore, oral therapy suffers from the inevitable drawback that the onus for taking the drug regularly rests on the patient, and inevitably a proportion of patients, when in therapeutic remission, fail to appreciate the necessity for regular maintenance therapy.

Pernicious anæmia is one of the few serious diseases in which perfect health can be maintained by careful treatment and it is therefore quite unjustifiable to depart from a regime of established efficacy if so doing entails an element of risk or uncertainty.

Non-Addisonian megaloblastic anæmias.—In this country this group of anæmias is relatively rare: in my clinic during the past five years 24 cases were seen as compared with 140 cases of Addisonian pernicious anæmia. In the general population the ratio is probably considerably less. It is nevertheless important that these cases be recognized when they do occur and that appropriate treatment be given. It must be appreciated that the operative deficiency may be in either cyanocobalamin or folic acid, or both.

Megaloblastic anæmia of pregnancy or the puerperium, in temperate climates, is almost always due to folic acid deficiency, and it responds satisfactorily to treatment with synthetic folic acid (pteroylglutamic acid) given by mouth in doses of 10 mg. twice daily. In severe cases blood transfusions are advisable if the time available is inadequate for the correction

of the anæmia before delivery. Once a normal picture is attained in the puerperium subsequent treatment is unnecessary, although patients should be observed carefully during subsequent pregnancies lest the anæmia recur.

Next to pregnancy, the commonest cause of non-Addisonian megaloblastic anæmia is *malabsorption from the alimentary tract*. This may be due on the one hand to demonstrable structural deformities such as gastro-colic fistula, developmental abnormalities of the intestine, or infiltration of the intestines by tuberculosis or reticuloses. On the other hand, it may result from the functional disorders, sprue, idiopathic steatorrhœa and cœliac disease. In the majority of these cases the essential deficiency is in folic acid, and this substance is indicated therapeutically. In some cases, however, cyanocobalamin may be lacking, whilst in others there may be a dual deficiency. Where facilities for the appropriate biological assays are available the precise nature of the deficiency may be determined before treatment is started. In the absence of such facilities, reliance must be based on therapeutic trial, administering each vitamin independently in the first instance. In megaloblastic anæmia due to steatorrhœa, a trial with a gluten-free diet is always worth while. Although the most brilliant results with this treatment have been obtained in young children with cœliac disease, in which the anæmia is usually of the iron-deficiency type, complete clinical and hæmatological remissions have occasionally been obtained in adolescents and adults with steatorrhœa associated with megaloblastic anæmia.

Megaloblastic anæmia following gastrectomy usually resembles Addisonian pernicious anæmia, in that it is caused by lack of intrinsic factor and consequent inability to assimilate extrinsic factor. Permanent treatment with parenteral cyanocobalamin is consequently indicated.

Megaloblastic anæmia due to malnutrition is uncommon in temperate climates, but occasional cases are seen in food cranks. The deficiency may be in either cyanocobalamin or folic acid, or both.

During recent years attention has been drawn to the occasional occurrence of megaloblastic anæmia in patients taking *anticonvulsant drugs* such as phenytoin sodium and primidone. These cases have usually responded to treatment with folic acid. The causative drug should, of course, be withdrawn. It is believed that the drug acts as a folic acid antagonist.

HÆMOLYTIC ANÆMIAS

Experience during recent years has served to confirm the value of steroid therapy in certain types of acquired hæmolytic anæmia, and its ineffectiveness in congenital acholuric jaundice and other hereditary hæmolytic anæmias. It is impossible to lay down rigid criteria for the recognition of cases of acquired hæmolytic anæmia likely to benefit from steroid therapy, but as a guide the Coombs test is of value since a favourable result may be expected in the majority of cases giving a positive reaction, whilst this is unlikely when the test is negative. In favourable cases a substantial degree

of remission may be expected within two or three weeks. In some cases, especially in acute 'idiopathic' cases, the remission will be permanent after discontinuing treatment, in others permanent maintenance therapy may be necessary. In this last group splenectomy should be considered, since the results are sometimes very satisfactory. In view, however, of the uncertainty of the value of this operation in acquired hæmolytic anæmias, it is advisable that steroid therapy should be tried in the first instance.

Cortisone has largely been supplanted by prednisone or prednisolone in hæmatological therapeutics, since undesirable side-effects are thereby reduced. It is advisable to begin with big doses such as 40 mg. daily in divided doses at six-hourly intervals and, if a favourable result is obtained, to try the effect of gradually reducing the amount until the minimal effective therapeutic dose is ascertained. It is generally advised that patients on prolonged treatment be given an injection of corticotrophin at weekly intervals in order to stimulate adrenal cortical activity.

Although the diagnosis of hæmolytic anæmias in an active phase is usually straightforward it may be difficult in chronic and subacute cases, especially in examples of so-called hypersplenism. In this connexion, the development of techniques for the estimation of red-cell survival times, employing cells 'tagged' with radioactive chromium, has proved to be of considerable value. This procedure has consequently become established as a regular diagnostic aid in many hæmatological clinics.

REFRACTORY ANÆMIAS

This title serves to designate a heterogeneous group of conditions failing to respond to the usual therapeutic measures. It includes anæmias due to diverse causes such as infections, toxæmias and neoplasia.

For the most part blood transfusion provides the only prospect of amelioration, but there is evidence that occasional cases may show a beneficial response to cobalt, given by mouth in the form of cobalt chloride in enteric-coated tablets in doses of 20 mg. three times daily. In my clinic two patients with moderately severe anæmia associated with chronic nephritis responded favourably to treatment with this drug. Cobalt should never be given indiscriminately since it is liable to cause gastro-intestinal disturbance.

THE LEUKÆMIAS

Many chemotherapeutic agents have been produced since the war, but none has proved to have more than a palliative effect in the treatment of leukæmia.

Chronic myeloid leukæmia.—For the treatment of this condition the choice probably lies between irradiation and busulphan, a cytotoxic drug given by mouth in tablet form. In general these two forms of treatment are of equal efficacy, and both require careful clinical and hæmatological control. In a given case the choice will probably be determined by the facilities available. Busulphan is usually given in daily doses of 1 to 4 mg., according to body

weight, until the white cell count falls to about 20,000 per c.mm. Like all cytotoxic substances it is dangerous and overdosage must be avoided.

Chronic lymphatic leukæmia.—For most cases irradiation is still the treatment of choice. An inferior alternative is nitrogen mustard given in saline intravenously, or in its oral form, tretamine. In this type of leukæmia it is particularly important to avoid over-treatment. One should be guided by the clinical state of the patient rather than by the white cell count.

Acute leukæmias.—Young children are much more amenable than adults to therapeutic remission, and remissions of up to a year or more may be obtained in a substantial proportion of cases, whereas in adults they seldom exceed a few weeks. The most useful drugs are the steroids, and mercaptopurine, an antimetabolite given by mouth in tablet form in a daily dose of 2.5 mg. per kg. body weight. Steroid therapy, in cases in which it is beneficial, usually produces its effect within a few days, but mercaptopurine may take six weeks before noticeable benefit occurs. Consequently, steroid therapy should be employed in the first instance in seriously ill patients. Prednisone or prednisolone is the preparation usually preferred and is given in doses similar to those recommended for acquired hæmolytic anæmia. Some physicians give mercaptopurine along with the steroid, whilst others prefer to reserve it until the steroid loses its effect. In early cases in good clinical condition treatment may be started with mercaptopurine.

The folic acid antagonists, such as aminopterin, are not often used now because they are usually less effective than the agents already mentioned, and are liable to produce severe toxic effects on the alimentary tract. They are, however, worth trying in children failing to respond, or who have ceased to respond, to the steroids and mercaptopurine.

Apart from drugs, blood transfusion and antibiotics still provide the basis for the palliative control of acute leukæmia. Investigations are in progress in a number of centres into the therapeutic possibilities of normal bone marrow transfusions following total irradiation, but this is still very much in the experimental stage.

POLYCYTHÆMIA VERA

Where the necessary facilities are available radioactive phosphorus (P^{32}) is probably superior to irradiation in the control of this condition. The isotope is given intravenously, usually in a single dose which can be repeated at intervals of six months to a year, or longer. The diagnosis and therapeutic control of polycythæmia may be materially facilitated by estimations of the total body red cell mass using red cells tagged with radioactive chromium.

THE HÆMORRHAGIC DISEASES

Thrombocytopenia.—Steroid therapy is always worth trying since, in a high proportion of cases, it results in the bleeding stopping or being reduced. This favourable clinical effect, however, is usually not accompanied by a

significant rise in the platelet count. Nevertheless, in some cases of idiopathic (essential) thrombocytopenia steroid therapy may induce a complete remission, which may or may not persist on withdrawing treatment. In idiopathic cases, therefore, steroid therapy provides a valuable prelude to splenectomy, and may in some cases render this operation unnecessary.

Coagulation defects.—For the control of bleeding in *hæmophilia* and *Christmas disease* infusions of fresh frozen plasma provide the most effective measure generally available. It should be appreciated, however, that the beneficial effect is transient, lasting only a few hours, and that repeated infusions may be necessary. As an alternative, citrated blood may be used, but it must be fresh since the anti-hæmophilic globulin rapidly deteriorates on storage. The Christmas factor also deteriorates, but less rapidly. It has been found possible to produce concentrated anti-hæmophilic globulin from beef blood, but this has the grave disadvantage, being a foreign protein, of inducing a state of allergy in the patient within a few days of its administration, and can therefore never be given to the same patient on a subsequent occasion. Consequently the use of this substance must be reserved for patients in extreme emergency, such as an unavoidable surgical operation. To overcome this drawback attempts are being made to 'de-specify' the globulin. In the meantime it should be used only in exceptional circumstances. Concentrated anti-hæmophilic globulin is not effective in Christmas disease.

It is perhaps appropriate here to mention that under the auspices of the Medical Research Council an organization has been set up for the registration of all hæmophiliacs, and for referring them to appropriate regional centres where expert advice is available for the management and treatment of the complications and emergencies to which these patients are prone.

Fibrinogenopenia may occur as a rare hereditary defect, and more commonly in the course of an abnormal pregnancy. The most effective therapeutic measure is the intravenous injection of fibrinogen in solution which is usually obtainable from regional blood transfusion centres. If this is not available reconstituted dried plasma may be used as an alternative. It should be noted that dextran given as a plasma volume expander exerts a deleterious effect in fibrinogenopenia.

Anticoagulant therapy by means of dicoumarol and related drugs is now widely used in myocardial infarction and other conditions. When properly controlled it seldom results in dangerous hæmorrhage, but occasionally it becomes necessary to reverse the anticoagulant effect. It is now generally recognized that vitamin K_1, or its oxide, is an efficient antidote whilst the water-soluble analogues of vitamin K are unreliable in this respect. Vitamin K_1 suitable for oral or intravenous administration is available commercially. The dose is 10 to 50 mg. according to the severity of the case.

Bleeding due to overdosage of heparin is rare and may be controlled by the intravenous injection of 10 ml. of 1 per cent. protamine sulphate.

ADVANCES IN GASTROENTEROLOGY

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RESEARCH of great promise goes on in many directions towards the elucidation of the causes of gastroenterological disorders. The practical applications of such work in diagnosis and treatment are less striking, but steady progress continues, especially as regards surgical and diagnostic techniques and in biochemical methods. Important lines of investigation continue to emerge from epidemiological studies.

CAUSATION

Gastric cancer.—Gastric cancer has a mortality in Great Britain at least twice as high in men as in women, and the number of cases occurring in the lowest social scale is nearly double that in the highest. Certain areas such as the rural areas of North Wales, and certain countries such as Japan have been shown to have an abnormally high incidence, and certain occupations such as those connected with blast furnaces and steel works which are exposed to iron dust or to silica dust have also abnormally high rates. These factors point both to exciting causes of varying nature and to underlying constitutional factors which must be present in precancerous individuals. Aird and his colleagues (1953) have shown that a relationship exists between the blood group A substance and the actual site in the stomach at which a cancer occurs, whilst Billington (1958) has shown in the case of gastric ulcer that there is an excess of individuals of blood group A among those who have prepyloric ulcers compared with those who have ulcers elsewhere in the stomach.

Peptic ulcer.—Observations such as these relating to gastric cancer are also being followed up in relation to the causes of peptic ulcer. At the sixth conference of the International Society of Geographic Pathology held in Paris in July 1957 it was clear that many speakers believed that inborn genetic characteristics as well as external factors were involved. As with cancer an abnormally high incidence of gastric ulcer was reported from Japan, and in England Watkinson (1958) showed from a study of approximately 20,000 necropsies that ulcers were more commonly found in the north than in the south of England. A world survey, covering 40 countries, carried out by May (1958) failed to show any correlation between peptic ulcer and either occupation, diet, or stressful situations, and he and other speakers suggested that the role of emotional stress had been overemphasized. In one paper the authors concluded that 'the description of peptic ulcer as a psychosomatic affection is not a clarifying nor even a stimulating hypothesis' (Straub and Schornagel, 1958).

Studies have continued upon the role of the endocrine glands in causing peptic ulcer, particularly in relation to steroid therapy, and also in con-

nexion with that severe type of refractory ulceration which occurs in association with β-cell adenomas of the pancreas—the Zollinger-Ellison syndrome. It may be that the ulcerogenic action of steroids is due to local action on the gastric mucosa when they are taken orally, but it is more probable that in some way they sensitize the stomach systemically to unknown irritants. There is no doubt that patients receiving steroid therapy show a higher incidence of peptic ulcer than control groups, as well as an increased gastric secretion and uropepsin excretion in the urine.

The small intestine.—Gradually increasing knowledge of the mechanisms concerned in the sprue or malabsorption syndromes has shown that idiopathic steatorrhœa is in fact cœliac disease in the adult, and that the irritant which causes this 'enteropathy' is a polypeptide fraction from the amino-acid, gliadin, which is found in wheat and rye. It is now thought that cœliac disease may belong to the group of enzyme-deficiency diseases such as glycogen disease, or familial non-hæmolytic jaundice in which there is deficiency of a single enzyme preventing the liver from properly excreting bilirubin. From small-intestine biopsy material in cases of idiopathic sprue and cœliac disease, Shiner (1958) has shown that atrophy of the intestinal villi occurs which is not inflammatory, and which does not return to normal even when clinical symptoms disappear and apparent recovery takes place.

The liver.—In England alcohol is far less often a cause of cirrhosis of the liver than in France or North America. In France, Caroli (1958) believes that a wine consumption of under 1 litre a day never produced cirrhosis whilst a consumption of over 2 litres a day almost always did. In England the cause of many cases of cirrhosis still remains uncertain. In the West Indies, veno-occlusive disease of the liver is a form of cirrhosis in which centrilobular fibrosis occurs and which has recently been studied both experimentally (Hill *et al.*, 1958) and clinically. Bras and others (1957) have shown that certain plants drunk as medicines in the form of 'bush teas' are almost without doubt the cause, and it is likely that this work will provide increasing and important new knowledge on the detoxicating action of the liver and the effect of ingested substances as causes of hepatic disease.

DIAGNOSTIC METHODS

Biopsy.—Histological examination of tissue obtained by means of the jejunal biopsy tube devised by Shiner (1956, 1958) has provided a safe method of investigating disorders of the small intestine, and some valuable results have been obtained. The method has helped to elucidate the changes occurring for example in steatorrhœa, Whipple's disease and other diarrhœas. More recently an ingenious metal biopsy capsule, only 11 × 17 mm. in size, has been devised at the Walter Reed Hospital, Washington, which can be swallowed on a fine 2-mm. polythene catheter and which allows specimens to be removed at any site in the alimentary tract between the stomach and the ileo-cæcal valve (Crosby *et al.*, 1958).

Intestinal pressure recorders.—Even more ingenious is a small capsule

devised by Farrar and Bernstein (1958) for recording movements of the small intestine and colon. This is a cylindrical plastic container about 3 cm. long by 1 cm. in diameter which is swallowed, and requires no connecting wires or tubes whatever. It consists of a tiny radio transmitter, a replaceable battery, which lasts for twenty-four hours, and a pressure-sensitive diaphragm. Pressures in the lumen of the gut are transmitted by radio signals to a frequency modulation receiver and recorded on paper through an oscilloscope. The capsule is swallowed and passes through the alimentary tract without trouble.

Cytology.—Many reports have appeared during the past two years on the diagnostic value of exfoliative cytology of the alimentary tract. Most observers consider that examination of gastric washings or of smears obtained by gastric suction or abrasion are complementary to x-ray examination and perhaps gastroscopy, but several reports suggest that the method should be used routinely in the diagnosis of gastric lesions, whether benign or malignant (Fischman, 1958). A few enthusiasts even consider that exfoliative cytology is as accurate as radiology in the detection of gastric cancer. The method requires meticulous attention to detail, and examination of the slides is very time-consuming, though as a rule malignant cells are distinctive and easily recognized.

Cytological examination of the œsophagus is more accurate than that of the stomach, which requires very thorough lavage before the washings are collected, centrifuged and smeared. Colon cytology is far more uncertain owing to the difficulty of obtaining material free from fæces. Palmer and his colleagues (1958), reporting on the value of cytology in the diagnosis of cancer of the digestive tract, claimed that in their hands the technique was more accurate than radiology, and recorded 95 per cent. of carcinomas in œsophagus, stomach and colon as correctly diagnosed, with fewer than 1 per cent. of false positives.

Uropepsin.—The diagnostic value of the gastric fractional test meal is small and the procedure is not without difficulty and discomfort to the patient. Methods to overcome this by the use of swallowed cation-exchange resins which are dissociated in the presence of free hydrogen ions in the stomach have been devised in which the presence of the cation in the urine can be estimated with little trouble to the patient. The techniques involved are simple and a number of recent reports have appeared in the literature. Denborough and others (1958), at Oxford, using the quininium ('diagnex') test in 73 patients, conclude that this method gives results in satisfactory agreement with those of the single-dose histamine test meal, and that, when the question of possible achlorhydria is important, this simple test is a useful new aid in diagnosis.

Serum transaminase test.—It has been found that necrosis of liver cells is associated with an increase of the transaminase activity in the blood, and that the greater the degree of liver-cell damage the higher the level of serum transaminase. The test is thus a useful index of acute liver damage and is

likely to be used increasingly in the diagnosis of acute hepatitis. It may show a considerable rise above the normal early in the disease before jaundice appears, although it gives no indication of the exact type of liver disease present. It is of little value as a test of liver function in cases of portal cirrhosis, gall-bladder disease, or cancer of the liver. There is already a considerable literature upon this subject, both as regards liver disease (see Madsen *et al.*, 1958) and heart disease, but it seems clear that this test cannot replace existing accepted liver-function tests, although it has a useful function as an additional diagnostic and prognostic aid in certain cases, especially of acute hepatitis and hepatic necrosis.

RADIOLOGY

The continued use of intravenous cholecystography has shown certain advantages over the oral dye method, but reactions to the injection, though rare, have occurred in the form of asthma-like attacks, skin eruptions, diarrhœa, and vomiting. Newer techniques for oral cholecystography by means of a double or triple dose of 'telepaque', combined with restriction of fluids to obtain a maximum concentration of the excreted dye in the biliary tract, enable good visualization of the bile ducts as well as the gall-bladder to be obtained, so that a true cholangiogram results. Some radiologists regard these recent oral dye techniques as more satisfactory than intravenous cholangiography.

Trans-splenic portal venography has become almost a routine investigation in cases of cirrhosis of the liver since it enables portal vein thrombosis to be diagnosed, and is therefore an important precaution to be taken if any form of porto-caval operation is being considered. Some 10 per cent. of patients in whom splenovenograms are taken suffer some side-effects which may include urticaria or even extravasation of blood or dye into the peritoneum.

Considerable anxiety has been aroused since the Medical Research Council's report on radiation hazards, published in June 1956, as to the danger of repeated diagnostic x-ray examinations in man. The potentially dangerous types of examination are naturally those done in young people which may directly irradiate the gonads. Barium enemas are thus of more possible danger than x-rays of stomach and duodenum, but in general the risks from gastroenterological examinations are exceedingly slight. Nevertheless the profession has rightly reconsidered the criteria for undertaking repeated barium meal and other examinations of the alimentary tract, and it is worth re-emphasizing that radiological control of the treatment of duodenal ulcer is of little value; since the persistence of scarring and deformity of the duodenal cap makes radiological diagnosis of the healing or non-healing of an ulcer difficult—if not impossible. There has been some salutary re-thinking in recent months on the necessity or advantages of repeating x-ray examinations of the alimentary tract if the clinical evidence is fully and carefully assessed.

TREATMENT

Hepatic coma.—Since Sheila Sherlock described the treatment of hepatic coma in *The Practitioner* two years ago (Sherlock, 1956), further reports have been published giving encouraging results in this serious condition. The treatment is based upon the view that toxic nitrogenous substances are largely responsible for the coma and that these arise either from bacterial action in the intestine or from absorption of blood products following gastro-intestinal hæmorrhage. The treatment thus depends upon extreme reduction of protein in the diet and the use of broad-spectrum antibiotics to control intestinal organisms. Neomycin, in a dose of 4 to 10 g. daily, is the most suitable antibiotic as it is scarcely absorbed, but unfortunately it is still expensive. At the same time enemas are used to empty the bowel together with purgation with a suitable preparation such as senna. Evidence that hepatic coma is related to an increase in ammonia in the blood is still uncertain although some reports have shown a close correlation between blood-ammonia levels and the clinical progression of hepatic coma. On the other hand, the use of the amino-acid, arginine, or of glutamic acid therapeutically with the hope of detoxicating ammonia in the body has proved disappointing, and Sherlock and her co-workers report no clinical improvement from the use of intravenous sodium glutamate.

Shunt operations.—These operations have no place in the treatment of ascites, and even for the prevention or control of bleeding from œsophageal varices there is still some uncertainty as to their value. In general, end-to-side porto-caval anastomosis is felt to be the most useful type of operation and this has an operative mortality of between 7 and 15 per cent. Further bleeding seems to be prevented in most cirrhosis patients who survive the operation, but it is too early yet to assess fully the long-term results of this treatment as regards the portal hypertension itself and the ultimate prognosis.

Ulcerative colitis.—During the past year there has been considerable interest in ulcerative colitis, and the results of surgery continue to show remarkable improvement. There has been a fuller realization of the high incidence of pseudopolyposis in long-standing cases, and of the real danger of carcinoma arising which, when it does, is usually highly malignant and metastasizes early. Bacon (1958) gives figures from the literature for the incidence of carcinoma in patients who have had colitis for more than five years of between 9 per cent. and 45 per cent., his own figure being 28.2 per cent. in a group of 46 colectomized patients. One-stage colectomy is being undertaken more often, and with increasing success, some surgeons using hypothermia as an adjunct in anæsthesia with very low operative mortality. There is increasing agreement that too long persistence with medical treatment, even if the colitis is stationary, deprives the patient of his best chance of surgery and that there are in fact very few serious contraindications to operation. With good control of electrolytes and the use of antibiotics, the mortality of colectomy, both with and without permanent ileostomy,

even including the severest cases, is approximately 5 per cent. Bacon reports an over-all mortality of 2.7 per cent. and complete rehabilitation in 90 per cent. of his patients (over 200) surgically treated. The wonderful change in outlook for the severe ulcerative colitis patient who can now be restored to full working life by surgery is one of the most brilliant advances in treatment of recent years.

Corticosteroids.—In acute ulcerative colitis intravenous corticotrophin is probably the most valuable means of treatment; in less severe cases oral cortisone, 300 mg. daily by mouth, is generally used. Only about half the cases, however, are likely to respond really well. In milder cases rectal hydrocortisone may be used and, using water-soluble hydrocortisone hemisuccinate sodium, Truelove (1957, 1958) reports rapid remission in two-thirds out of 60 treatments. Retention enemas of this preparation are given once or twice in the twenty-four hours using 100 mg. of hydrocortisone in 100 ml. of normal saline run slowly from an ordinary infusion bottle through a catheter into the rectum. The results may be excellent and the enemas may be continued once daily for some weeks if they are clearly doing good, but cortisone treatment should not be maintained for long periods unless there is definite improvement. If surgery is decided upon, the treatment should be changed to corticotrophin. All steroid therapy is completely stopped during the last two or three preoperative weeks.

'*Salazopyrin*'.—This preparation has been very widely used in Scandinavia and the United States. Reports of successful results were given in London by Svartz, Bargen and others at the congress of gastroenterology in 1956 and more recently at Washington in 1958. The drug is an azo compound of salicylic acid and sulphapyridine ('azulfidine' or 'salazopyrin') and is given initially in a dosage of 3 to 5 g. daily, with a smaller dosage—1 to 1.5 g. daily—for longer periods if there is improvement. Severe intolerance or troublesome side-effects are not infrequent and may prevent the use of this drug altogether. In Great Britain 'salazopyrin' has been increasingly used recently and in my experience certainly justifies a trial even though in some cases it seems quite ineffective.

Antibiotics.—Sterilization of the gut can readily be obtained preoperatively and it has also been shown recently that this can be achieved post-operatively by giving antibiotics intraluminally. Many combinations of antibiotics have been tried, of which the mixture of tetracycline and neomycin has been very successful but, as with all such mixtures, the possible risk of resistant organisms arising must be remembered. Both the combination of penicillin and streptomycin, as well as the tetracyclines, may lead to the development of severe enterocolitis which is often due to a resistant staphylococcus. This condition is now well recognized and may present as a fulminating severe diarrhœa with gross dehydration and disturbance of electrolytes, and there may be extensive pseudomembranous formation in the intestine, with œdema, shock, and death. The risk of 'antibiotic' diarrhœa must be considered in any patient having a prolonged course of

antibiotics, and particularly in postoperative cases when antibiotics have been used prophylactically. Cook and others (1957) reported 31 cases, mainly due to *Staphylococcus aureus*, of which 14 died. Efforts to lessen the risks of these infections by the use of suspensions of lactobacilli have been continued with varying success.

NEW THERAPY

Overenthusiasm for new forms of treatment must not lessen the need for care in watching for side-effects or avoiding serious results. So-called tranquillizers have been widely used in nervous dyspepsia, for cases of peptic ulcer, for colon spasm and other conditions, and may produce untoward effects. *Chlorpromazine jaundice* is one well-recognized syndrome with serious, but fortunately not permanent, liver damage. The condition usually begins about fourteen days after starting the drug and is associated with prodromal fever, nausea and abdominal pains and about a week later jaundice which is obstructive in type. It is probable that the liver changes are due to hypersensitivity to the drug. As a rule recovery is complete soon after the drug is stopped. All such tranquillizing drugs must be used with great caution in patients with liver disease (Werther and Korelitz, 1957). Reports suggest that their action is little if at all more successful in nervous dyspepsia than other well-tried sedatives such as phenobarbitone or amylobarbitone.

Several new *anticholinergic drugs* have been introduced, but side-effects in the form of blurred vision, constipation or dry mouth are not infrequent. Their use in the treatment of ulcer must not take the place of orthodox rules of regime and diet and, in general, results in cases of peptic ulcer have been somewhat disappointing. Indeed, in one series a blind trial of two of these preparations showed no difference either in alleviation of subjective symptoms or in radiographic healing of duodenal and gastric ulcers as between the active drugs and an inert control preparation (Ihre, 1958).

CARCINOIDS AND SEROTONIN

Increasing interest has been shown in the clinical manifestations of argentaffinomas (carcinoids) of the gastro-intestinal tract, and in the study of serotonin which was first synthesized in 1951. Chemically this substance is 5-hydroxytryptamine (5HT). It is found mainly in the alimentary tract; and is produced in large amounts by carcinoid tumours. Incidentally, it is a main constituent of the venom of wasps and of stinging nettles. It seems likely that this substance plays an important role in the human body and recent work suggests that it may be concerned in the normal control of intestinal movements. It is found also in the central nervous system, and its relation to certain specific antagonists and to such alkaloids as reserpine has suggested that it may even play some part in mental disorders such as schizophrenia. Serotonin is a substance whose pharmacological activities may be expected to become more and more understood in coming years and may

well influence our views in gastroenterology and wider fields of general medicine in quite important respects.

Carcinoids have been fully described clinically, and are now accepted as actively or potentially malignant tumours which, as a rule, only cause general symptoms when they have already metastasized. The great majority occur in the appendix, the remainder arising in the ileum and jejunum or, much more rarely, in the colon. The most characteristic symptoms are a fiery flushing of the skin, particularly brought on by drinking alcohol, tachycardia, bronchial asthma and diarrhœa. Organic changes in the right side of the heart with pulmonary stenosis and tricuspid regurgitation occur which are due to the excessive production of serotonin. The diagnosis is extremely difficult before metastases arise, but the test for 5-hydroxyindole acetic acid (5HIAA) in the urine may show excessive output of this substance, and should be carried out in any patient showing atypical diarrhœa with skin flushes or asthma-like attacks. Unfortunately, treatment is disappointing and no specific antagonist to serotonin is yet available.

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ADVANCES IN PERIPHERAL ARTERIAL DISEASE

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RELIEF of obstruction of major vessels by surgical procedures has been more frequently and more successfully performed within the last few years, and this change has altered our management of peripheral arterial disease. There has been less advance in treatment of diseases of the small vessels. In this review therefore our primary consideration will be obstructive disease of the larger vessels: the internal carotid artery and the vessels of the lower limbs from the bifurcation of the aorta to the popliteal artery. Conventional therapy, aimed primarily at disease of the smaller vessels, is only briefly considered.

CLINICAL EXAMINATION OF PATIENTS

The severity and extent of arterial obstruction can usually be found by clinical examination and nowadays the practitioner should endeavour to ascertain whether the arterial obstruction is such that surgical relief is practicable. In general we choose for arterial surgery patients whose circulation is severely reduced, but who, as yet, have no breakdown of tissues. Occasionally, even if there is rubor of dependence or breakdown of tissue, an arterial graft may relieve the chronic ischæmia. Intermittent claudication to some degree is often present, but in itself is usually not an indication for direct arterial surgery. Surgery is indicated when the circulation to the foot is so jeopardized as to present a serious threat to the survival of the tissues.

Clinical examination, and in particular careful palpation of the pulses, will usually tell whether the obstruction is in large or small arteries, and whether it is localized or widespread. If pulsation is absent or diminished in one or both of the femoral arteries, the block is likely to be in the aorta or iliac arteries and merits an aortogram to show the level of the block. If the femoral pulse is normal and the popliteal pulse is absent, the block is likely to be in the femoral artery and a femoral arteriogram is indicated. These pulses should be palpated with the patient in the recumbent position with his leg muscles completely relaxed. The femoral pulse should be sought with the three central fingers together, the popliteal with both hands around the knee. If a good popliteal pulsation is present, but the distal

pulses are absent, the block is likely to be distal to the bifurcation of the popliteal artery, in which case arterial reconstruction is impracticable. An oscillometer serves to confirm the knowledge gained through one's fingers, but is not essential if the examiner is experienced in detecting pulsations.

In determining the severity of the reduction of circulation a vasodilatation test or a reactive hyperæmia test is used. The former consists of measurement of skin temperature of the toes when the patient's body is warmed and the feet are exposed to cool air. Such testing provides valuable information regarding collateral circulation to the feet, the prognosis of the limb, and so for the selection of one or another form of therapy. If the test is done in a 20°C. controlled temperature room, the skin temperature measurements may be used as an index of corresponding blood flow (Felder, *et al.*, 1954). The reactive hyperæmia test requires no special apparatus. The limb of the patient is first warmed by a water bath at 35°C., or by heating with pad and blankets. It is then elevated and stroked until it is pale, when a pressure cuff on the limb is suddenly inflated to a pressure greater than the systolic. The circulation is thus arrested for five to ten minutes during which time the limb is lowered and kept warm. With the limb in a good light, the pressure cuff is released and the spread of the flush is timed. If the circulation is normal the flush spreads over the whole foot and toes in ten seconds, but when arterial disease is present the flush is delayed and faint in proportion to the severity and extent of the disease.

Final preparation of the patient for surgical treatment differs considerably from that adopted ten years ago. Then it seemed important to decide to what degree the circulation could be improved by removal of vasomotor tone, for sympathectomy was the most effective available form of surgical treatment. Accordingly, a vasodilatation test was performed and vasomotor tone was reduced by heating the patient, by spinal anæsthesia, or by sympathetic nerve block, in order to observe how much relief of vasoconstriction occurred. Now the important investigation is arteriography which is quickly carried out, and shows the extent of the obstruction better than any other method. From it the surgeon can discover whether the vessels distal to the one that is to be repaired are of wide enough calibre to permit an adequate 'run-off', for, if the flow of blood through the repaired segment is slow, thrombosis is more likely to occur within it.

Three examples of arterial disease merit special mention.

POPLITEAL ANEURYSM

Popliteal aneurysm is to be suspected when the patient gives a history of recurrent episodes of ischæmia in a foot. In other cases the diagnosis can be made when there is pain or discomfort in a popliteal space, and a pulsating mass is palpated. Many popliteal aneurysms, however, are painless and remain undetected. Such aneurysms are not always recognizable by palpation, and oscillometry may be required to help in diagnosis. Arteriography is advisable for definitive diagnosis and exact localization. A clot is usually

demonstrated in the aneurysm. When the diagnosis is established the popliteal space should be explored surgically. If the thrombus in the aneurysm is recent or not complete the aneurysm can usually be successfully replaced by a graft. When the aneurysm or clot has involved the bifurcation of the popliteal artery, grafting is not feasible, but even in these cases ligation and excision of the aneurysm may prevent further extension of the thrombus in important collaterals, and thus save the leg.

INTERNAL CAROTID ARTERY OBSTRUCTION

Internal carotid artery obstruction has been more frequently recognized since the report of Eastcott, Pickering and Rob (1954) that the condition can be treated surgically. Many patients who previously would have been considered to suffer from cerebral thrombosis are now correctly diagnosed as having obstruction of the carotid artery. The obstruction is usually localized between the origin of the internal carotid artery and the skull and is amenable to surgical correction. The characteristic history is of repeated transient disturbances of cerebral function: hemiplegia, loss of vision, paræsthesia, or dysphasia, with complete recovery in the interim. In most cases the underlying pathological lesion is atheroma.

Demonstration of lack of pulsation in the affected artery is a definite diagnostic sign, but one which is difficult to be sure of. Externally, it is impossible to distinguish between pulsation in the common carotid and internal carotid arteries, so that pulsation of the internal carotid must be felt from the mouth. The pharynx is cocainized and pulsations felt for behind the pillars of the fauces. When there is stenosis, rather than occlusion, a bruit may be heard. Manual occlusion of the artery on the unaffected side may give rise to syncope and convulsions, so the syndrome may be confused with 'carotid sinus syndrome'. Demonstration of reduced systolic pressure in the retinal artery of the affected side provides strong evidence of internal carotid obstruction. An encephalogram, with the patient on a tilt table, may further help the diagnosis. Arteriography before operation is very desirable, although some authorities consider that surgical exploration of the artery carries less risk. Often the block can be dealt with by thrombo-endarterectomy, but occasionally resection of the affected portion of the artery is required and a graft may have to be inserted.

NEUROVASCULAR COMPRESSION SYNDROMES OF THE SHOULDER GIRDLE

Neurovascular compression syndromes of the shoulder girdle are the cervical rib, scalenus anticus, costoclavicular, and pectoralis minor syndromes, and combinations of these such as the hyperabduction syndrome. Gradual progress has been made in treatment of these disorders (Lord and Rosati, 1958). The brachial plexus and the axillary artery come together at the thoracic outlet, and pass anterolaterally over the first rib behind the insertion of the scalenus anticus muscle; they then pass between the clavicle and the first rib to enter the axilla behind the tendinous insertion of the pectoralis

major muscle. The subclavian vein takes the same route except that it passes in front of the insertion of the scalenus anticus tendon on the first rib. Wide motions of the shoulder, anatomical variations, and sometimes disease, may subject the neurovascular bundle to compression at various points; hence the variety of syndromes. Different manœuvres of the shoulder and neck serve to detect them, different exercises to alleviate them, and different surgical procedures to cure them.

Differential diagnosis of these cases from herniated cervical disc, cervical arthritis, cord tumour, and exostosis of the laminæ is usually possible. Compression syndromes often involve artery or vein whereas the others do not; compression syndromes usually involve the eighth cervical and first thoracic roots, the others involve higher or multiple roots, and so the distribution of the pain differs. When diagnoses other than those of pure neurological syndromes have been excluded and the symptoms are severe, surgical exploration should be undertaken. Sometimes a local stenosis of the subclavian artery is found as in carotid artery disease.

GENERAL TREATMENT

The general principles underlying the treatment of peripheral vascular disease remain unchanged. Peripheral blood flow may be increased by relief of vasomotor tone, which is done by warming the body of the patient rather than the affected extremity. Measures designed to increase the peripheral flow by local increase of arterial pressure continue to be useful: Buerger's exercises serve for home treatment, but in hospital the use of an oscillating bed ensures that the therapy is more constantly carried out. The greatest increase in the blood flow and in the supply of oxygen to ischæmic feet has been obtained by maintaining a considerable foot-down angle of the bed (20°) for at least five minutes during each cycle of oscillation (Forno, Montgomery and Horwitz, 1958). The oscillating bed requires so little supervision that it has largely replaced treatment by intermittent suction and pressure except in the cases of acute thrombosis or embolism.

MEDICAL TREATMENT

Vasodilator drugs are numerous and should be tried in resistant cases. It is a good rule that all patients with peripheral arterial disease should avoid the use of tobacco because of the vasoconstrictor effect of nicotine. In thromboangiitis obliterans tobacco appears to have a specific effect in exacerbating the disease and, since a firm stand has been taken that all patients with this disease must avoid its use, fewer amputations have been required.

Ethyl alcohol, the pharmaceutical component of a variety of beverages, is as effective an oral peripheral vasodilator as any. The main disadvantages of its use are its soporific and psychological effects, which may be better tolerated in older patients. It is prescribed to be taken before luncheon and dinner, and before retiring, in a form and dosage suitable to each patient. It is unsuitable for young patients, those in whom there is danger of addic-

tion, and those who have objections to its use. Very old patients should take only small, well-diluted doses.

Several competitors of alcohol have proved to have nearly equal vasodilator properties. Two examples are tolazoline and phentolamine. These are given in tablet form, in doses of 25 to 50 mg. thrice daily. Both are sympatholytic and adrenolytic agents, and have the additional advantage of local vasodilator action by reason of the imidazole nucleus of histamine. The vasodilator action is principally in the skin of the hands and feet. No known vasodilator drug is as effective as thorough body warming and the success of drug therapy is enhanced if the patient keeps reasonably warm. The prevalence of chilblains, however, shows how difficult it can be to persuade English patients to keep themselves adequately warm. Tolazoline has a vasoconstrictor effect on the blood vessels of resting muscles, buphenine ('perdilatal'; 'arlidin') is said to have a vasodilator effect in resting skeletal muscle, but there is no indication that it or any other drug adds to the vasodilator action of muscular exercise. In cases of intermittent claudication encouragement of the patients to live within the limitations of their disease is of primary importance.

Steroid treatment is of benefit in vascular disease only when the disorder is associated with one of the collagen diseases. In systemic lupus erythematosus and polyarteritis nodosa the beneficial effects of steroid therapy may be temporarily very useful. In dermatomyositis and systemic scleroderma the local lesions are seldom improved, and such beneficial effects as do occur may be attributed to the antipyretic, euphoric, and appetite-stimulating actions of the drugs. In this group steroids are usually given as prednisone or prednisolone. Treatment is started with a high dosage (up to 50 mg. daily) and thereafter decreased, the dosage and duration of the therapy being limited to the amount necessary to control symptoms.

Anticoagulants have been used for years in the treatment of phlebitis with recurring embolism. Now more patients with severe grades of chronic arterial occlusion are being given anticoagulants over a prolonged period in the hope that occasional thromboses and gangrene may be prevented. After surgical treatment of major arterial obstruction anticoagulant therapy is often prolonged to guard against the danger of delayed thrombosis within the repaired vessel.

Heparin sodium, being available in as high concentrations as 20,000 units (approximately 200 milligrams) per ml., is now suitable for subcutaneous injection. Intravenous administration is probably still the most effective but requires professional attendance. Intramuscular injection usually causes some discomfort. There is a growing tendency to use larger doses of heparin with longer intervals between doses: for example, 10,000 units subcutaneously every twelve hours. It is a good plan to start with 5000 units intravenously every six hours for several doses, then to use the subcutaneous route with the same schedule and gradually adjust the dose until the clotting time immediately preceding each injection is about twice that before treat-

ment was started. The dose can then be doubled and given every twelve hours, still by the subcutaneous route. If a fine needle, an inch (2.5 cm.) in length, is used, heparin can be given for many weeks with little discomfort. Intelligent patients can be taught to administer the drug to themselves after the physician is confident of the correct dose.

Dicoumarol is still widely used. The method of its administration remains essentially unchanged. Plasma prothrombin is determined prior to the first dose. If it is normal (70 to 100 per cent.), 300 mg. of dicoumarol are administered orally to an adult of average weight, 200 mg. are given on the next day and 100 mg. on the third. Prothrombin should be determined daily; it usually falls to the desired 20 to 30 per cent. of normal by the fifth day, but occasionally it may fall sooner. The daily maintenance dose is usually between 50 and 75 mg. When the prothrombin level has been maintained at 20 to 30 per cent. of normal for a week, the interval between its determinations can be increased, so that usually by the third week it can be every three days, and by the fifth week every seven days.

Phenindione has a more rapid effect than dicoumarol, and maintains a depressed prothrombin level more steadily than ethyl biscoumacetate. It is administered orally twice a day. A total of 150 to 200 mg. is given on the first day, and subsequent doses are designed to maintain the prothrombin level between 20 and 30 per cent. of normal.

In most cases it is still advisable to administer heparin until the longer acting anticoagulant has exerted its full effect. In prolonged anticoagulant therapy a prothrombopenic agent is usually deemed necessary, although sometimes heparin is found to be superior.

Fibrinolytic agents have become available for investigation in more purified and less toxic forms during the past year. In the laboratory these preparations have the property of lysing clots which are not more than a day or two old. In practice they are given by slow intravenous infusion to patients with recent thrombosis of the major vessels. So far the therapeutic effect of these infusions has not been great. The problem is to get a sufficiently high concentration of the substance to the thrombus. This is difficult to achieve with non-toxic doses. It would seem to be more effective to inject the fibrinolytic agent directly into the thrombosed vessel, and this has been done at operation with apparent softening of the clot. The use of these agents for the relief of venous thrombosis may possibly be attended with the danger of dislodging clots to form pulmonary emboli. Further investigation of fibrinolysins is well worth pursuing in the hope of producing more satisfactory results.

SURGICAL TREATMENT

In recent years brilliant advances have been made in the direct surgical attack on chronic obstructions of arteries. In general, the larger the diameter of the artery and the shorter the obstruction, the more successful is the operation likely to be. Short obstructions may be relieved by thromboendarterectomy or resection of the affected segment. When the occlusion is

extensive, thromboendarterectomy may sometimes be successful but usually some form of graft is required. Autogenous veins, homografts, or woven synthetic materials may be used as grafts. It is not yet known which type of graft is the least liable to subsequent thrombosis, and further investigation of the after-history of patients, as well as animal experiments, is needed.

Unfortunately, postoperative thrombosis occurs often within the cleared segment, or in other parts of the arterial tree. This occasionally happens during operation, or shortly thereafter, but may take place after some months or years. Continuous anticoagulant therapy may be used to guard against thrombosis but at the risk of hæmorrhage at the site of operation or elsewhere. For this reason we have hesitated to advise the routine use of prolonged anticoagulant therapy following operation.

The less frequent use of sympathectomy may be attributed to a wider appraisal of its limitations rather than to its replacement by direct arterial surgery. Sympathectomy for the relief of arterial disease of the upper limb is now recognized as a disappointing measure. In a recent review (Gifford, Hines and Craig, 1958) less than half of the patients were found to have benefited from the sympathectomy which had been performed, and some had been made worse. In the lower limb sympathectomy has proved more effective when the disease is present mainly in the small vessels of the feet, for example as in early thromboangiitis obliterans and perhaps collagen arteritis and livedo reticularis; it is less useful when the obstruction is in major vessels; it has not been proved to be effective in the treatment of intermittent claudication. Since sympathectomy is effective mostly in disease of small vessels, and arterial surgery is applicable only to the larger vessels of the thigh, the two forms of treatment can be considered as complementary to each other.

CONCLUSION

In certain patients the newer surgical methods have yielded brilliant results hardly conceivable a few years ago. It is always well to remember, however, that the most striking developments cannot be employed for the majority of patients who have arterial disease, and that older principles of therapy continue to have much value. In this connexion, the importance of hygienic care of ischæmic extremities should be explained in detail to the patient, for his understanding of the precipitating factors of injury is still an important part of preventive medicine. Furthermore, when dealing with elderly and debilitated patients we must recognize the limitations of the newer techniques, and not subject our patients to unreasonable dangers of reparative procedures. We should remember that on occasion amputation is the wiser choice.

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ADVANCES IN THE TREATMENT OF TUBERCULOSIS

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During the past decade the problem of writing a succinct and up-to-date account of advances in the treatment of tuberculosis has been beset by formidable difficulties. The revolution in therapy, begun in 1944 by the discovery of streptomycin, had gradually gathered momentum and had swept forward at such a pace that the ink was scarcely dry upon the paper before changes in clinical practice had invalidated what had been written. Our mental reorientation to the new concept was retarded by a natural scepticism regarding therapeutic short-cuts in this most disabling of chronic diseases, but time and clinical experience have ironed out many of the uncertainties and much that would have been considered speculative and daring in 1955 can now be set down as established fact.

BASIC PRINCIPLES OF TREATMENT

It is under this heading that the full extent of the therapeutic revolution which has taken place is most apparent. Formerly the subject would have been approached via the triad of bed rest, adequate diet and fresh air with collapse therapy, surgery and chemotherapy cited as adjuvants to 'the sanatorium regime' which remained the sheet anchor of all treatment. Today, treatment is based on the employment of antibacterial substances of proven efficacy against the tubercle bacillus and the main task of the physician is to ensure that these are used correctly, that the choice of drugs is the best possible for the individual case, that the appropriate dosage is prescribed and that treatment is sufficiently prolonged to secure full and permanent control over the infection. All other methods of treatment now play a secondary role and are employed when indicated and not as a routine.

STANDARD ANTI-TUBERCULOUS CHEMOTHERAPY

The admirable series of trials carried out by the Medical Research Council in Great Britain, and by the Veterans Administration in the United States, has provided much information on the proper use of the standard anti-tuberculous drugs and has indicated how their abuse may be avoided. Modern treatment is based largely on the results of these trials and excellent accounts of current practice have been given by Crofton (1957) and Ross (1958). It is generally accepted that chemotherapy must be combined, continuous and prolonged, and the following combinations of drugs and dosages are known to be effective against normally sensitive strains of bacilli:

(1) Streptomycin, 1 g. daily, with isoniazid, 100 mg. twice daily.
(2) Sodium PAS, 5 g. twice daily, with isoniazid, 100 mg. twice daily.
(3) Streptomycin, 1 g. daily, with sodium PAS, 5 g. four times daily.
(4) Streptomycin, 1 g. three times a week, with isoniazid, 100 mg. twice daily, and sodium PAS, 5 g. twice daily.

It will be noted that the above statement is qualified by the proviso *normally sensitive strains of bacilli*. The importance of this proviso cannot be overemphasized, for bacillary resistance to any of the standard drugs may wreck completely the most carefully planned regime. The results of sensitivity tests are seldom available at the start of treatment but a careful history, which must include a detailed account of the pattern of any previous chemotherapy, should make it possible to assess the likelihood of resistance. For example, a story of single drug therapy over an appreciable period or the employment of two drugs intermittently will at once suggest the possibility that resistant organisms are already present. In the patient who has not previously been treated the occurrence of primary resistance due to infection by a drug-resistant strain must be kept in mind, especially when there is known contact with a sputum-positive case who has received chemotherapy or when the patient resides in an area where it had been customary to prescribe chemotherapy in combinations later recognized as unsatisfactory. When the history, clinical or environmental, suggests that drug resistance may be present, arrangements should be made for sensitivity tests and until the results of these are available all three standard drugs should be given daily. Any adjustment in the regime indicated by the sensitivity results can be made later.

When normal sensitivity of the organisms can be presumed or has been proved the physician can select any one of the four combinations mentioned as his initial line of attack. All are therapeutically effective but those containing isoniazid appear to have a slight advantage and, in the absence of any specific contraindication, it is advisable always to include isoniazid in the treatment programme.

DRUG TOXICITY

None of the standard drugs is free from toxic effects, the occurrence of which may necessitate a revision of the plan of treatment.

Streptomycin.—The commonest manifestation of streptomycin toxicity is disturbance of the vestibular mechanism due to damage to the eighth nerve. It has been suggested that the concurrent administration of pantothenic acid, 50 mg. thrice daily (Ducrot *et al.*, 1956; Penman *et al.*, 1957), reduces the incidence of vestibular damage but the evidence so far is not completely convincing and for the present any symptoms suggesting vestibular dysfunction should be accepted as an indication for stopping streptomycin. Hypersensitivity to streptomycin occurring within the first month of treatment is not uncommon and is marked by fever, with or without a rash, although the rash may occur alone. It is a sound working rule to regard any rise in temperature during the four weeks following the start of chemotherapy

as due to drug hypersensitivity until proved otherwise, and all drugs should be stopped at once until the fever has subsided. Thereafter a test dose of streptomycin should be given; if this provokes a febrile reaction, a course of desensitizing injections should be begun. Occasionally the reaction is so severe that desensitization has to be carried out under steroid cover.

Isoniazid enjoys an advantage over both streptomycin and PAS in that its efficacy is paralleled by a remarkable freedom from toxicity in ordinary dosage. The toxic effects so far observed have been centred almost entirely on the nervous system, the commonest being peripheral neuritis (Robitzek and Selikoff, 1952), whilst convulsions, optic atrophy and major psychoses have also been reported. Such occurrences, however, are rare on the dosage usually prescribed and it is estimated (Committee on Therapy of the American Trudeau Society, 1953) that in only about 1 per cent. of cases are they sufficiently severe to contraindicate treatment. Care should be used in administering isoniazid to alcoholics and its employment in epileptics has been shown to increase the number of fits (Biehl and Nimitz, 1954).

PAS exercises its chief toxic effect on the gastro-intestinal tract, the commonest symptoms being nausea, vomiting and diarrhœa. When used in a dosage of 5 g. twice daily these symptoms are seldom sufficiently severe to justify the suspension of treatment, and adjustment may be achieved by a change in the method of administration. A patient who fails to tolerate liquid PAS may find it acceptable in the form of cachets or enteric-coated tablets or granules. Hypersensitivity to PAS is fairly common and is usually characterized by fever and a rash. Differentiation from hypersensitivity to streptomycin may confuse the issue at first, but suspension of treatment followed by a test dose will clarify the situation and when hypersensitivity has been proved desensitization should be carried out.

VARIATIONS IN STANDARD CHEMOTHERAPY

High-dosage isoniazid.—In the trials conducted by the Medical Research Council the amount of isoniazid employed was 100 mg. twice daily and this has since remained the usual dose in British practice. The adequacy of this dose has been questioned by American workers (Mandel *et al.*, 1957). It has been shown that isoniazid is metabolized in the body by an acetylation mechanism which also renders it therapeutically inactive and there is evidence suggesting that the rate of acetylation varies appreciably in different individuals. It follows therefore that a patient who metabolizes his isoniazid rapidly may be unable to maintain an adequate blood level of the biologically active drug, with resultant loss of therapeutic effect and increased risk of the development of drug resistance. The concurrent administration of PAS slows down the rate of isoniazid metabolism by competing in the body for the same acetylation process and may thus assist indirectly in the maintenance of an adequate blood level (Johnson, 1954). In addition, Kass *et al.* (1957) have advocated the use of large doses of isoniazid (16 mg. per kg. body weight) to counteract any excessively rapid

inactivation. With this regime they have obtained an effective therapeutic response and by giving pyridoxine, 100 mg. daily, have been able to eliminate or control any neurotoxic side-effects resulting from the high dosage.

Corticosteroids with chemotherapy.—Initially the presence of active tuberculosis was considered a contraindication to the use of corticosteroids in treatment (Freeman *et al.*, 1950; Hart and Rees, 1950). Subsequently this view was modified and there is now evidence that when combined with adequate anti-tuberculous chemotherapy the corticosteroids may be used with safety and in certain circumstances may have an important part to play in treatment (Cochran, 1954; Houghton, 1954). A controlled trial on the use of prednisolone in the treatment of pulmonary tuberculosis has been carried out by the Research Committee of the Tuberculosis Society of Scotland (1957), and analysis of the results has shown that the treated cases, especially those who were acutely ill, showed a more rapid clinical response than the controls, whilst during the first two months of treatment the radiological response was also significantly hastened. From the evidence at present available it would seem that corticosteroids may be employed with advantage in seriously ill patients to secure a more rapid alleviation of acute symptoms and toxæmia and, in addition, they are indicated in cases of severe drug hypersensitivity in which desensitization is likely to be difficult. So far there is nothing to suggest that they have any part to play in the routine treatment of pulmonary tuberculosis.

ALTERNATIVE ANTI-TUBERCULOUS DRUGS

There are no completely satisfactory alternative drugs yet available for the long-term treatment of tuberculosis in cases which are resistant to standard chemotherapy. There are, however, a number of substances possessing some degree of anti-tuberculous activity which may be used for short periods to deal with specific problems and emergencies arising from drug resistance.

Viomycin.—This drug is less effective than either streptomycin or isoniazid but has sufficient bacteriostatic action to provide a reasonable cover for resection surgery. It is considerably more toxic than the standard drugs but in the usual dosage of 1 g. twice daily on two days each week toxic side-effects are now relatively rare. Resistance to viomycin will develop if it is given alone and it may be combined with oxytetracycline given in the unusually high dosage of 4 to 5 g. daily. Even on this dosage the onset of resistance may merely be delayed.

Pyrazinamide.—This drug, an analogue of nicotinamide, is also less effective than either streptomycin or isoniazid. It can be given by mouth but has the grave disadvantage of high toxicity. Liver damage is particularly common and the incidence of severe hepatitis is in the region of 5 per cent. Bacillary resistance appears rapidly when pyrazinamide is given alone and is not delayed by oxytetracycline. There is, however, considerable experimental and clinical evidence (McDermott *et al.*, 1954; Schwartz and Moyer, 1954; Phillipps and Horton, 1956) to suggest that its antibacterial action is greatly

enhanced when isoniazid is given concurrently, and in cases resistant to streptomycin and PAS the advantages of a pyrazinamide-isoniazid regime probably outweigh the disadvantages of increased toxicity.

Cycloserine.—Cycloserine is about equivalent to pyrazinamide in antituberculous action and has a similar high toxicity. Neurotoxic side-effects are common and may include major convulsive episodes and even frank psychoses. It is administered orally in doses of 0.5 to 1.5 g. daily and, although it has been shown that on a dosage of 0.25 g. twice daily toxic manifestations are almost eliminated (Walker and Murdoch, 1957), it seems probable that the clinical benefits are correspondingly reduced. The place of cycloserine in treatment has yet to be defined but its toxicity suggests that the field for its employment is likely to be severely restricted.

It must be emphasized that these alternative drugs are very much a 'second best' and are only indicated when two or more of the standard drugs cannot be employed. They are unsuitable for prolonged treatment, and it is therefore essential that they should be combined with all other measures, including surgery, which may assist in bringing the tuberculous disease under control.

RESULTS OF CHEMOTHERAPY

The results produced by the modern practice of prescribing prolonged courses of daily chemotherapy have been impressive and the hopes which had been based on the theoretical possibilities of this line of attack have now been largely fulfilled. Recent reports (Ross *et al.*, 1958; Crofton, 1958) have demonstrated that, when the bacilli are drug-sensitive and treatment is sufficiently prolonged, it is possible to secure control over the disease in practically all cases and to reduce the relapse rate to negligible proportions. Ross and his co-workers, following up a series of cases admitted to hospital in 1953, have shown that the major factors contributing to relapse are drug resistance and inadequate duration of treatment, and they draw attention to a group of 63 patients, all with sensitive organisms, who received more than eighteen months' continuous treatment and in whom no instance of relapse has occurred. Additional encouragement for the future is derived from the knowledge that the development of drug resistance under adequate and prolonged antibacterial treatment is extremely rare (Crofton, 1957) and its occurrence in such circumstances suggests either a departure from the regime prescribed or the presence of some degree of resistance preceding the start of treatment. The claims that chemotherapy, properly employed, can rapidly render the infectious case sputum negative, can cut short the period in hospital and can permit a more rapid and safer return to normal life and work appear to be amply justified and are rendering superfluous the provision of rehabilitation and vocational training courses which were formerly regarded as the culmination of treatment.

DURATION OF CHEMOTHERAPY

The optimum duration of antibacterial treatment is still undetermined but

evidence is gradually accumulating which suggests that eighteen months' continuous administration is the minimum likely to be effective. Courses of two to four years are indicated in patients with extensive pulmonary changes of considerable standing, whilst in cases of far advanced disease who have been rendered sputum negative chemotherapy may require to be continued indefinitely if their non-infectious status is to be maintained.

TRADITIONAL METHODS OF TREATMENT TODAY

The success of chemotherapy necessitates a reappraisal of the part to be played now and in the future by the non-specific forms of treatment traditionally associated with tuberculosis.

Bed rest.—Whilst an initial period of bed rest is still essential for the seriously ill and toxic patient, its usefulness in the afebrile patient with a relatively limited lesion is now being questioned. A number of studies have been reported (Tyrrell, 1956; Weir *et al.*, 1957; Kay, 1957) in which patients treated by bed rest plus chemotherapy were compared with control groups receiving chemotherapy alone. The results did not suggest that bed rest had any significant beneficial effect. Kass *et al.* (1957) have pursued the matter a stage further. They argue that since there is good evidence to show that the bactericidal action of streptomycin and isoniazid is only exercised against bacilli which are in a state of metabolic activity and are actively multiplying (Middlebrook and Yegian, 1946; Schaefer, 1954; Singh and Mitchison, 1954), bed rest may be a disadvantage in that the reduction of bodily activity tends to force the organisms into a metabolically dormant state in which they are unaffected by chemotherapeutic agents. They suggest that it is more rational to encourage bacillary proliferation in order to obtain the maximum benefit from the drugs and that, as the aerobic tubercle bacilli require oxygen in which to flourish, an adequate supply may be ensured by the increased pulmonary movement and improved cavity drainage which accompany physical activity on the part of the host. Kass and his colleagues have carried their theories into practice over the past four years and the satisfactory clinical results which they have obtained suggest that their concept is worthy of further consideration.

Collapse therapy.—The success of chemotherapy has relegated collapse therapy to the pages of history. It is difficult now to think of any circumstances in which therapeutic lung collapse is either indicated or justifiable.

Lung resection.—The introduction of the antibacterial drugs made the excision of tuberculous lung tissue a safe, practicable and popular proposition. As the possibilities of prolonged drug treatment have become apparent, however, the necessity for surgical intervention has declined. Present trends suggest that ultimately surgery will be utilized only in the chemotherapeutic failures. Resistance to the standard drugs has already become the chief indication for resection. The surgical removal of residual nodular foci as a safeguard against relapse has been almost completely abandoned and even persistent cavitation is no longer an automatic target for surgery.

Two factors have contributed to this more conservative attitude towards cavitation. The first was the observation that, contrary to all previous beliefs and teachings, a proportion of patients with cavitated lesions who were unsuitable subjects for major surgery remained well and non-infectious on long-continued drug treatment (Douglas and Horne, 1956; Corpe and Blalock, 1958). The second, which is supported by pathological and bacteriological findings, is the discovery that with chemotherapy open healing, i.e. healing of the internal surface of the cavity without obliteration of its air-containing lumen, is no longer a clinical rarity. The possibility of such a process is suggested when serial x-rays show progressive thinning of a cavity wall which finally takes on a 'hair-line' appearance giving an impression of elasticity more characteristic of cystic change than active tuberculosis. The whole question of the significance of these residual 'cystic' cavities has been the subject of intensive investigation (Johnsen and Hewitt, 1954; Bernard and Carraud, 1954; Brun *et al.*, 1954; Keers *et al.*, 1956; Altmann and Diaz, 1958; Wilson *et al.*, 1958) and the evidence so far suggests that the majority represent true tuberculous cavities whose walls, having shed their caseous and necrotic lining, are undergoing fibrous healing. There is no reason to suppose that such open healing when complete will not give a satisfactory end result and the mere presence of an intrapulmonary air-containing space on an x-ray is no longer a signal for immediate surgical action.

Hospital treatment.—Although the success of chemotherapy has eliminated the need for the sanatorium with its traditional regime of prolonged bed rest followed by graduated exercise, hospital treatment is still necessary for the majority of patients with pulmonary tuberculosis. It is generally agreed that the toxic case, the case with complications and the infectious case all require admission to hospital until constitutional symptoms have disappeared and the sputum has been sterilized. Opinion varies, however, regarding the management of the non-infectious and afebrile patient. In theory such a patient could perfectly well receive his chemotherapy at home, but human fallibility has to be taken into account and it has been shown that irregularities of dosage and of regime occur more readily at home than in hospital (Dixon *et al.*, 1957; Wynn-Williams and Arris, 1958). Furthermore, all the standard drugs can produce toxic side-effects, usually fairly early in the course of treatment, which may have dangerous and alarming possibilities unless promptly recognized and treated. In the patient's home recognition and treatment may be delayed.

Circumstances undoubtedly justify home treatment in individual cases but as a general rule an initial stay in hospital of at least two months is advisable. During this period the patient's tolerance to his drugs can be assessed and the vital importance of taking them regularly and in full dosage can be impressed upon him.

Rehabilitation.—The elimination of sanatorium treatment of tuberculosis has for practical purposes disposed of the never very adequately solved problem of rehabilitation. The physical and mental 'softness', the atmosphere

of over-caution and the gradual drift into a semi-vegetable existence which sanatorium treatment tended to foster created the necessity for rehabilitation but the more dynamic approach to treatment made possible by chemotherapy has produced a healthier attitude of mind in both physician and patient. Tuberculosis is no longer 'a dread malady' but has become an incident in life which, although often necessitating a temporary interruption of immediate activities and plans, need have no more far-reaching effects. As soon as the clinical and radiological evidence indicates quiescence of the lesion the patient may be allowed to return to a normal working life and, whilst he should be left in no doubt about the necessity for continuing his chemotherapy, his pleasure in his restored health should not be marred by tedious and unnecessary precautions and restrictions on his freedom. Only in the most exceptional circumstances should it be necessary to advise a change of occupation.

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ADVANCES IN THE TREATMENT OF CANCER

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THE world literature covering the research work and clinical experimentation on the treatment of cancer is vast and it would be impossible and unprofitable to attempt to cover it in this article. The practitioner, however, must be aware of the major advances that have been made and of the alterations in the direction in which various methods of cancer therapy are progressing. The choice of the best method of treatment is his and he must be able to steer a well-balanced pathway in guiding the treatment of his patient between the controversial methods often proposed by distinguished specialists in this field. It is the purpose of this article to point out those changes now regarded as definite advances and to indicate alterations in the trend of treatment of various forms of cancer.

THE CURATIVE CANCER OPERATION

The principle of excision of the primary growth, together with as much surrounding tissue as is practicably possible, and of the immediate lymphatic drainage area *en bloc* still holds good. An increase in the anatomical extent of these operations has been made possible by improvement in the ancillary services available to the surgeon. It might be hoped that more extensive operations which include even larger areas of lymphatic drainage might improve the prognosis. Technical advances in anæsthesia, in the art of blood replacement, and in the understanding of the electrolyte and hormone disturbances that are associated with major surgery have permitted these operations to be carried out. The pathologist, by careful observation of the natural progression of the spread of disease, has been able to indicate to the surgeon the extent to which, and direction in which, they should be enlarged. In assessing their value certain questions should be asked.

Is the associated mutilation and the disturbance of the normal physiological mechanisms of the body a justifiable price for the patient to pay for a 'cure'? Improvement in surgical technique has done much to diminish these unpleasant side-effects of surgery. For example, in the operation of pelvic viscerectomy the miseries of a wet colostomy need no longer be endured. It is possible to form a bladder from short segments of either ileum or colon and thereby enable the patient to collect the urine in a

Rutzen bag type of receptacle. Equipped in this way these patients may carry out a normal and active working and social life.

Apart from the increase in mortality rate are there any other dangers associated with these operations? Extended heroic cancer surgery in which dissection is carried out through, or close to, malignant tissue may be harmful. The operation may disseminate tumour cells to distant sites through the blood stream and also locally in the wound field. The nutrient medium organized by the body to facilitate wound healing proves ideal for the establishment and growth of these cells and hence the development of local wound recurrences. How may such disasters be prevented? Adequate selection of the patient for super-radical surgery is essential. The biological behaviour of the particular tumour must be considered. Tumours which, although extensive in local spread, have shown a slow growth pattern are more suitable than those in which the growth rate is rapid and the natural history of the disease, if untreated, would be short. In the latter cases, even if the local disease can be cleared by the operation, it is likely that distant metastatic spread will have occurred already. At no time should cancer tissue be cut across and the possibility of seeding into the wound be allowed to occur. In large bowel surgery the frequency with which cell implants in the anastomosis line occur may be diminished by washing out the rectum and colon as a first stage in the operation. In other areas of the body, such as radical neck dissections or radical mastectomy wounds in which large areas are exposed to cell implantation, a similar technique of washing the wound before closure has been adopted, at times using cytotoxins, and there is evidence that the incidence of local recurrences is decreased. Free cancer cells can be demonstrated in the blood stream at the time of surgery. In an attempt to render them non-viable cytotoxins have been administered parenterally before, during, and after the operation.

Are the results of super-radical surgery any better than those obtained by the standard adequate cancer operation? The initial wave of enthusiasm for these procedures has been replaced by a more cautious viewpoint. Experience has shown that in certain areas the extended operation has a very real place as a therapeutic tool. This applies particularly to pelvic viscerectomy for advanced local disease arising from carcinoma of the cervix. In the head and neck, carcinoma of the posterior third of the tongue is best treated by excision of the lesion together with an *en bloc* in-continuity radical neck dissection on the side of the lesion. Similarly, when the disease has spread to the lymphatic glands, the operations of laryngectomy and pharyngectomy should be carried out as an in-continuity dissection with the appropriate radical neck dissection. It is doubtful whether an improvement in the prognosis can be obtained when such operations are applied to carcinoma of the breast or carcinoma of the stomach or to other abdominal viscera.

In the case of certain organs, as good results, together with a decrease in the associated morbidity, have been obtained by more conservative

rather than more extensive operations. In large bowel surgery the operation of anterior resection together with conservation of the lower rectum and the anal canal in suitably selected carcinoma of the intraperitoneal upper part of the rectum or rectosigmoid will give results equal to those obtained by the orthodox combined abdomino-perineal excision of the rectum. Similarly, the results of lobectomy or even sleeve resection of the bronchus with conservation of the distal lung in suitable cases of bronchogenic carcinoma will give as good or better results as those obtained by pneumonectomy. The results of partial gastrectomy and omentectomy, if adequate clearance of the tumour-bearing area is obtained, will yield as high a cure rate and less morbidity than a total gastrectomy when the carcinoma does not involve the cardia.

ENDOCRINE ABLATIVE SURGERY

Orchidectomy and oöphorectomy are well-established methods in the treatment of carcinoma of the prostate and breast respectively. More recently, bilateral adrenalectomy and hypophysectomy have been used in their treatment. The results obtained with carcinoma of the prostate are not satisfactory but with carcinoma of the breast considerable improvement, with halting of the disease and regression of metastases, may be seen in those cases which respond. At the present time it is impossible to state whether hypophysectomy or adrenalectomy is the more effective procedure in treating mammary cancer. Objective improvement making these operations worth while for the patient occurs in about sixty per cent. of cases. In half of these the improvement is dramatic. Accurate selection of those cases likely to respond is still not possible but, when osseous metastases are present, the changes observed in the urinary calcium excretion rate when a hormone stimulation test or cortisone suppression test is carried out can be used as an index of hormone dependence. Those tumours shown to be hormone dependent, or to have responded to previous hormonal therapy, may be expected to benefit from these ablative endocrine operations. It is becoming increasingly apparent that they should not be withheld until the terminal stages but should be employed earlier in the natural history of the disease.

Finally, it must be stated that removal of these endocrine glands may in some cases be a meddlesome procedure leading to a hormonal imbalance suitable for enhanced tumour growth rate, and therefore by carrying out these operations a disservice has been done to the patient.

RADIOTHERAPY

Apparatus.—Sources of supervoltage radiation are becoming more readily accessible to the radiotherapist. Supervoltage x-ray machines, betatrons, theratrons, linear accelerators and high specific intensity radioactive sources of cobalt-60 or cæsium-137 provide sources of irradiation by which a precise homogeneous dose may be delivered at a definite volume. By rotating

either the patient or the source of irradiation, it is possible to confine the maximum dose to a very circumscribed volume, and to deliver a high depth dose without causing appreciable skin reaction. This permits a more efficient treatment of malignant disease arising in organs deeply situated, such as the œsophagus or bladder, than could have been obtained by previous methods of therapy. At the same time the associated morbidity is reduced. Critical evaluation of the results obtained by such treatment, however, is disappointing. Despite the administration of adequate cancericidal doses the improvement in prognosis has not been great.

Some metals, made radioactive in the atomic pile, provide advantages over the techniques, already well established, in which radium needles or radon seeds are used as sources of interstitial irradiation. Tantalum wire treated in this way may be threaded through a tumour in the base of the bladder at cystotomy and after the correct dosage has been delivered can be removed through the urethra. Gold grains rendered radioactive can be implanted into the tumour. These have the economic advantage in that if not used they can be returned and once again rendered radioactive in the atomic pile. Although the radiotherapeutic advantages of radioactive isotopes have not been as great as was initially expected, they may still be used effectively in the treatment of certain forms of malignancy. Radioactive colloidal gold is effective in controlling effusions when the metastatic lesions are two millimetres or less in thickness. Thus, it is particularly useful in the treatment of pleural effusions and may also prove to be the method of choice with multiple superficial mucosal malignancies of the bladder. Generalized osseous metastatic disease from carcinoma of the breast has been shown to respond to a combination of treatment with testosterone propionate and radioactive phosphorus. The results obtained in the use of radioactive iodine in the treatment of thyroid carcinoma are disappointing. Relatively few thyroid carcinomas with metastases concentrate this substance in sufficient quantities for it to be effective.

Radiobiology.—The main emphasis in radiotherapy is shifting to the exploration of the radiobiological aspects of the tumour. If the tumour tissue can be rendered more susceptible to irradiation without increasing the vulnerability of the normal tissues of the tumour bed, still further improvement in the results of radiotherapy may be anticipated. There are indications that the intracellular homeostasis may be altered by biochemical measures and that there are enhancing effects of irradiation due to certain endogenous products such as thyroid, adrenocorticoids, œstrogens and androgens. These hormone effects do not appear to be directly related to any hormone-dependent properties of the tumours. Many agents with proven chemotherapeutic effects against various types of malignant cells have been shown to have enhanced results when combined with irradiation. Improved results have been obtained in the irradiation of carcinoma of the bronchus when the patient has been receiving 'synkavit' injections and has been breathing oxygen under increased pressure. Combinations of nitrogen mustard and

irradiation are reported to give better results in the treatment of malignant lymphomas than when either treatment is carried out alone. A similar enhancing effect is seen when actinomycin D is given together with irradiation.

CHEMOTHERAPY

Large numbers of chemotherapeutic agents have been synthesized and developed during the past fifteen years, and passed into the hands of the research workers who have tested them for their effect on cellular function and their toxicity to the host cells. As a result of this screening process, the majority of substances have had to be discarded but a few substances have been established as effective and safe therapeutic agents if selected carefully and given by those trained in their use. Three main groups of substances are available and the scope of this article will only permit a general summary of their use.

(1) *The alkylating agents.*—The best known and most widely effective agent in this group is the *bis* form of nitrogen mustard. Other agents such as tretamine, thioTEPA, chlorambucil, and busulphan have all proved their use in the clinical field. These agents are used mainly in the treatment of chronic leukæmias and in the lymphoma group of diseases. Experience has shown that differences in action of these drugs makes certain of them more suitable for the treatment of one disease than another. For instance, nitrogen mustard is most effective in the treatment of the terminal stages of the lymphoma group, whereas tretamine and chlorambucil are useful when given as long-term agents in the treatment of the chronic leukæmias. The mechanism of action of these substances, as yet not clearly understood, is probably a direct alkylation of the cell components. This process is very similar to that produced by ionizing radiation, in which mitotic division is impaired and chromosome morphology is altered.

(2) *Antimetabolites.*—The most widely used and effective agents in this group are 'aminopterin', methotrexate, and mercaptopurine. These agents are of main use in the treatment of the acute leukæmias. They act by competition with normal cell metabolites. Their structure is sufficiently similar to the normal metabolites used in cellular metabolism for them to be incorporated in the cell and replace the normal substances. As a result, the normal metabolic pathways become distorted or blocked and the growth of the cell is impaired.

(3) *Antibiotics.*—A large group of these substances is in the trial phase of experimental use. As yet, few have become generally available to the clinician. Of these, actinomycin D has been shown to be effective in the treatment of soft-tissue sarcomas and some epithelial tumours such as carcinoma of the breast.

Principles of treatment.—The margin of safety is small between the dosage of these chemotherapeutic agents necessary to be effective against the cancer and that dose which will cause depression of the hæmopoietic system

and the development of an aplastic bone marrow. The result obtained depends upon the skill with which the clinician can exert the maximal effect on the tumour while at the same time preserving bone marrow function. A new method of using these agents has been reported. In the case of certain tumours it is possible to isolate the blood supply of the tumour-bearing area, often an extremity and, by using a pump oxygenator system, viability of the limb or organ can be maintained while at the same time it is perfused with high concentrations of chemotherapeutic agents. At the end of the perfusion time the normal limb or organ blood supply is re-established. Using such a technique, concentrations of these agents sufficient to destroy the cancer cell can be given and yet the normal host tissue cells remain undamaged. The temporary isolation of the blood supply perfusing the limb or organ prevents the escape of the agent into the circulation and general bone marrow depression does not occur. Much further work needs to be done with this technique but this approach may open up new possibilities in which cancer chemotherapy may be applied more effectively to a wide variety of tumours.

HORMONE THERAPY

Considerable experience has been gained in the use of hormones in the treatment of cancer. Cancer of the breast and prostate are the two epithelial tumours which are hormone stimulated and respond to hormonal therapy. The operations of bilateral adrenalectomy and hypophysectomy have been discussed already. The use of œstrogen in the treatment of prostatic cancer and of œstrogens and testosterone in the treatment of breast cancer is well established and need not be discussed here. The use of cortisone or prednisone in the treatment of these two diseases has now passed from the trial phase and has been proved to be effective. In carcinoma of the prostate, prednisone will produce remissions in approximately fifty per cent. of cases. In carcinoma of the breast objective remissions manifest by healing of osseous lesions, lowering of urine calcium excretion rate, lowering of serum calcium levels, and the control of soft-tissue disease may last for many months or even years. Some centres have found this treatment so effective that this form of suppression of adrenal function is used in preference to the operation of bilateral adrenalectomy. The question as to when prednisone therapy should be used in the treatment of the disease poses a problem which only the experience of the clinician can solve. It is a growing belief, however, that its use should not be withheld until the terminal stages of the disease are reached but rather that it should be used as soon as there is evidence of metastatic disease.

Steroid therapy has been shown to be effective in the treatment of the lymphoma group of diseases. Striking remissions have been obtained with the use of large doses of prednisone in the treatment of the terminal stages of Hodgkin's disease. Lysis of the high swinging temperature, the clearing of jaundice, and the shrinkage of palpable soft-tissue glandular involvement

may all be seen but unfortunately these remissions are short, lasting only two to three months.

COMBINED THERAPY

A combination of chemotherapeutic agents may be more effective than the use of individual drugs. Similarly, the sensitivity of a tumour to irradiation may be increased by the simultaneous use of one or more of these chemotherapeutic agents. Some tumours respond better to irradiation or to chemotherapy when the treatment has been combined with the use of steroids. All these methods of treatment have one common factor: the disturbance of the normal physiological activity of the cancer cell. This may be achieved by the direct alkylation of cell constituents such as the nucleoproteins, by the direct competition of antimetabolites and the blocking of essential metabolic pathways, by the interference of the normal vital enzymatic reactions by alteration in the hormonal milieu of the cell or by the effect on mitotic activity and chromosome structure produced by ionizing radiation. Although differences exist in the exact site and mode of action of all these methods of treatment they have a synergistic action when used in combination.

It has been established that improved results may be obtained when radiation is added to surgery in the primary treatment of certain forms of cancer. It is probable that preliminary irradiation, such as is used in the treatment of osteogenic sarcoma, so alters the viability of the cancer cell that these cells, if disseminated locally in the wound or through the bloodstream by subsequent surgery, will be incapable of undergoing metastatic growth. With combined therapy it may be possible to use a number of these agents which, in the concentrations used, would be non-toxic to the host cells and would not depress the mechanisms of immune response of the body and yet would, in combination, so effect the metabolism of the cancer cell that it would not survive if spread by the surgical procedure.

SUMMARY

Advances in the treatment of cancer have been made in all the major fields of therapy, but critical assessment of the results obtained indicates that there is little justification for complacency. Although much has been achieved in affording the patient good palliation and enabling him to live in comfort with the disease, the long-term survival or 'cure' rates have shown little improvement. Perhaps the most significant advance has been the clinician's appreciation that larger operations and more complex and powerful therapy machines do not, of necessity, confer better treatment on the patient. Assessment of the differing biological potentials of each individual cancer has led to a more careful selection of the appropriate form of treatment. Surgeon, radiotherapist, and chemotherapist are appreciating that the future of cancer therapy lies at the cellular or intracellular level and are directing their efforts and attention accordingly.

ADVANCES IN NUTRITION AND DIETETICS

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'ADVANCES in nutrition' was last dealt with in this series by Professor Cruickshank in 1952. In this article he discussed mainly problems of the nutritive value of proteins in lower animals and man, protein deficiency in the form of kwashiorkor, and the nutritive value of cereals. In the same issue Professor Robert Platt discussed obesity, and there was an unfortunate reference elsewhere to the work of the Birmingham group on cœliac disease in 1952 as being 'original work of the highest standard' whereas in fact it confirmed the earlier Dutch work. In the limited space of this review only a few topics can be selected, and I shall confine these to problems related to the metabolism and therapeutic uses of fats. We may start with the Dutch work just mentioned.

STEATORRHŒA

The myth that cœliac disease might be caused by intolerance to fat and carbohydrate was destroyed when Dicke (1950), and then Weijers and van de Kamer (1950), showed the dramatic effect of treating cœliac children with diets free of wheat or rye. This was soon confirmed by Frazer's group in Birmingham (Anderson *et al.*, 1952) and others (Sheldon and Lawson, 1952). The Dutch workers then showed that if cœliac children who had recovered on a wheat-free diet were fed the gluten from wheat, their condition rapidly deteriorated (Dicke, Weijers and van de Kamer, 1953). Cases of adult idiopathic steatorrhœa also respond to a gluten-free diet, but such recovery is much slower than in children (French, Hawkins and Smith, 1957). Details of gluten-free diets have recently been provided by Fletcher and McCririck (1958).

There is no evidence that tropical sprue responds to this dietetic therapy. This condition is associated with rancid fat in the diet. Rancid fat will cause diarrhœa and death in rats (Burr and Barnes, 1943) and also steatorrhœa (French, 1949). The latter does not believe that deficiency of essential fatty acids (EFA) can be the cause since the diarrhœa occurs within a day or so of the feeding, and he attributes it to some factor in the rancid fat that causes an excess of mucus secretion by an irritant action. This does not dispose of a local deficiency of EFA, and I have found that rats deficient in EFA are much more sensitive to the diarrhœic effect of rancid fat, and that this effect can be abolished by simultaneous administration of EFA with an antioxidant (tocopherols); further, feeding rancid fats decreases the content of EFA in the epithelium of the gut. The essential fatty acids are certain highly unsaturated ones and rancidity implies oxidation of these with formation of a hydroperoxide which itself is a strong oxidizing agent. I

believe it is the oxidative action of these hydroperoxides that causes a local deficiency of essential fatty acids in the gut-wall with consequent damage. Sensible therapy for tropical sprue would seem to be the elimination of rancid fat from the diet and administration of a lecithin rich in EFA, together with an antioxidant.

OBESITY

Before discussing essential fatty acids further, we may consider the treatment of obesity. This is one of the major therapeutic problems in medicine today. There are various reasons why it should be actively combated: it represents a considerable danger to health since it is well known that the expectation of life decreases with increasing obesity mainly because chronic degenerative diseases become more prevalent; it represents a waste of food—since obesity indicates an increased intake relative to expenditure—and of energy since the obese carry out every movement with more work than in the case of the non-obese; it represents a danger to the health of others since accidents are commoner in the obese; it is unæsthetic.

It is obvious that obesity must represent a greater absorption of calories from the gut than expenditure of calories in energy (work and heat). Therefore obesity might be caused either by eating more than is eaten by a non-obese person of the same sex, age, size and activity, or by obese persons having a lowered activity or decreased metabolic rate. Mayer and his colleagues (Johnson, Burke and Mayer, 1956) studied 28 obese and 28 non-obese girls matched for age and height; the obese girls ate considerably less (2000 calories daily as compared with 2,700 calories) and were much less active. This conforms with a common observation that thin persons are active and tense (the 'lean and hungry look'), whereas obese persons lie relaxed in armchairs; but exceptions are numerous. Mayer also studied mill-workers in West Bengal (Mayer, Roy and Mitra, 1956) and found that caloric intake varied with physical activity only when the total activity was above a certain level; below this level the less the activity the more the intake. This result has been confirmed on rats. From these and other studies the conclusion arises that the treatment of obesity is to decrease caloric intake and increase physical activity. There is general agreement that the intake of protein should be relatively high and, of course, the specific dynamic action of this increases caloric expenditure at the expense of fat and carbohydrate. No amount of exercise will achieve reduction in obesity unless attention is paid to diet, which should not exceed 20 cal. per kg. of ideal body weight with protein providing about a quarter of the calories and carbohydrate supplied mainly in the form of bulky fruit and vegetables of low-carbohydrate content. A fairly active housewife whose height is 62 inches (158 cm.) and ideal weight 120 lb. (54.5 kg.), and who would normally require to absorb from the gut about 2,500 calories daily, would therefore receive about 1,120 calories daily with 70 g. of protein, 40 g. of fat and 120 g. of carbohydrate. This provides 25 per cent. of the calories from protein, 32 per cent. from fat and 43 per cent. from carbohydrate. Pharma-

ceutical preparations may be used to decrease the appetite. Thyroid preparations should not in general be used, but amphetamine sulphate (5 to 10 mg. half an hour before meals) is useful except in ischæmic heart disease.

The ratio of carbohydrate to fat needs further consideration. Since fat in the diet is an economical form of calories, in that fatty foods in general contain little bulk or water and provide more than twice the calories of an equal weight of pure carbohydrate, it is generally believed that fatty foods should be avoided; further, they are expensive. Pennington (1954) has revived the diet applied to William Banting whose letter on corpulence was published nearly a century ago; he was the patient of a Dr. Harvey who believed the obese person could not use carbohydrate which therefore became stored as fat. Hence there have lately appeared certain ephemeral pamphlets that advise the public to eat as much as it likes provided carbohydrate is avoided. Pennington's view is that 'obesity, in most cases, is a compensatory hypertrophy of the adipose tissues, providing for a greater utilization of fat by an organism that suffers a defect in its ability to oxidize carbohydrate'. He believes that a common cause of obesity is an impaired ability of the tissues to oxidize pyruvic acid which is known to come from the breakdown of carbohydrate in the tissues. Therefore not only is the oxidation of carbohydrate prevented but the pyruvic acid that accumulates inhibits the oxidation of fat. On this view blood pyruvate of the resting obese person should be raised, and the basal metabolic rate should be decreased; neither of these facts has been established. On the other hand, Kekwick and his colleagues (Kekwick and Pawan, 1956, 1957; Chalmers, Kekwick and Pawan, 1958) have obtained evidence that during very short periods (one week) high-fat diets may cause loss of weight. Basal metabolic rates did not appear to be altered and, according to the authors, the loss of weight could not be attributed to loss of body-water; this is an important point since diets high in carbohydrate cause retention of water in the body and those high in fat cause loss of water.

The treatment of obesity by allowing diets containing unlimited fat and restricted carbohydrate needs further investigation before it can be recommended to the public on sure physiological grounds. This criterion may be thought unimportant if in practice it works, but the evidence for this is not conclusive. There is a much more important reason why it cannot as yet be recommended: it may be a very dangerous form of treatment. High-fat diets in this country mean diets high in relatively saturated fat and relatively deficient in essential fatty acids. Before returning to this we may consider obesity in children from a dietetic standpoint.

INFANTS AND CHILDREN

Improved nutrition of pregnant and nursing mothers and of their infants is the major factor responsible for the greatly decreased infant mortality which is one of the great triumphs of modern medicine. Further, rickets and scurvy are now rare diseases. But, as I have pointed out elsewhere (Sinclair, 1957),

we have been too complacent in admiring the Welfare Foods scheme which was put on such a sure footing by Sir Wilson Jameson during the war. Orange juice is not necessarily the best way of administering ascorbic acid (vitamin C); blackcurrant juice would probably be a much better source. Cod-liver oil is a bad vehicle for vitamins A and D in view of the absence of essential fatty acids from it and the presence of non-EFA fats that increase the need for EFA. Cow's milk, and particularly dried cow's milk if exposed to air, is very inferior to human milk.

Passing to children, we may note that the School Meals and Milk-in-Schools schemes were far-sighted policies that have improved the health and physique of schoolchildren; the School Meals scheme can also play an important part in educating the child in good dietary habits. But during the past ten years I have been cautioning against the overfeeding of children, particularly with cow's milk and butter (Sinclair, 1955, 1957). Excessive feeding during the period of maturation is likely to lead to early maturity and to early death from chronic degenerative diseases. Excessive use of cow's milk and butter may lead to deficiency of essential fatty acids.

ISCHÆMIC HEART DISEASE

It is impossible here to give any but the briefest outline concerning the nature and metabolism of essential fatty acids (EFA) and their possible role in the causation of coronary thrombosis. I have given short summaries elsewhere (Sinclair, 1957, 1958a). The two most important EFA are linoleic and arachidonic acids which are fatty acids with 18 and 20 carbon atoms respectively; they are unsaturated in that linoleic acid has two double bonds in its carbon chain and arachidonic acid has four. Arachidonic acid occurs in no plant source and in few animal foods, but it can be formed in the body from linoleic acid if vitamin B_6 (pyridoxine) is present. Linoleic acid forms about half of certain vegetable seed oils such as maize (corn) oil, groundnut oil and wheatgerm oil; processed olive oil is a poor source. Unfortunately EFA are very unstable, oxidation with ultimate rancidity occurring in presence of air; vitamin E (tocopherol) is a natural anti-oxidant that preserves the linoleic acid in vegetable-seed oils. EFA also occur in certain animal foods; certain fish oils (but not cod-liver oil) are good sources, but the fat of ruminants (cows, sheep) contains little and therefore butter is a poor source and cow's milk contains very much less than does human milk. These facts are undisputed. Controversy, however, surrounds the need for EFA in the human body and the results of deficiency. The controversy is ventilated in the proceedings of an international Conference on EFA recently published (Essential Fatty Acids, 1958), and this contains the evidence for, and references to, most of the following statements.

Atherosclerosis and coronary thrombosis are in general rare in underprivileged countries and increasingly common in countries such as this. There is evidence from work on lower animals that a fat-free diet will cause EFA-deficiency and the inclusion of non-EFA fat (such as saturated fat)

will cause a much more serious deficiency. What is important for our purposes is the ratio of EFA-fat to non-EFA fat, and this ratio becomes increasingly unfavourable as foods are increasingly processed and sophisticated. Coronary thrombosis has been produced in rats on diets that contain butter or cod-liver oil (both rich in non-EFA fat and poor in EFA) but not if maize oil (which is rich in EFA) is substituted. Highly unsaturated fats (such as EFA) lower serum cholesterol in people subsisting on diets such as ours, whereas saturated fats (non-EFA) raise serum cholesterol; this is largely the work of Kinsell, Ahrens, Malmros, Bronte-Stewart and their colleagues (Essential Fatty Acids, 1958). There is no conclusive evidence that high serum cholesterol causes atheroma; elsewhere (Sinclair, 1958a) I have briefly stated the case for deposition of cholesterol in various sites in the body occurring through failure of the tissues to use the cholesterol they are forming because of a relative deficiency of EFA (or low ratio of EFA-fat to non-EFA fat) in those tissues. This failure of utilization and metabolism of cholesterol could cause a rise in serum cholesterol. EFA appear to be required for fibrinolysis which is essential for removing clots that are regularly forming intravascularly. Decreased fibrinolysis, perhaps also accompanied by increased coagulability of blood, could account for coronary thrombosis in presence of atheroma.

The rapid increase in notified deaths from pulmonary embolism and infarction, which is occurring in this country at the same rate as deaths from ischæmic heart disease, could be similarly attributed to a relative deficiency of EFA. This deficiency causes a structural defect in cell membranes and connective tissue, and the body in consequence becomes increasingly susceptible to injurious agents. Among these are infections, ultra-violet light, x-rays, chemical carcinogens and hydrochloric acid in the duodenum. It is possible therefore that a relative deficiency of EFA could play a part in the etiology of coryza and poliomyelitis by allowing the virus to traverse the mucous membranes of nose and gut, of leukæmia, of lung cancer and of duodenal ulcers. In lower animals deficient in EFA the matrix of bone is defective causing easy fractures, and this could be related to senile osteoporosis, another disease that is increasing at the same rate as is ischæmic heart disease. The requirement of EFA in lower animals is about seven times greater in males than in females during the reproductive period. This fits the incidence of the diseases mentioned.

PRACTICAL IMPLICATIONS

Kinsell (Essential Fatty Acids, 1958) has reported therapeutic success in the treatment of intermittent claudication with maize oil as a source of EFA. Work on lower animals strongly suggests that the deposition of cholesterol in tissues can be removed by administration of EFA and that maize oil (which is rich in EFA) will prevent coronary thrombosis even if saturated (non-EFA) fat is included in the diet. In the present state of knowledge it seems sensible to treat hypercholesterolæmia, severe atheroma and myo-

cardial infarction with diets high in EFA-fat and low in non-EFA fat; obviously I am only referring to dietetic treatment in general; various factors that increase the requirement of EFA (e.g. hypothyroidism, diabetes mellitus) may be present. A fat-free diet has the effect of increasing EFA-deficiency since the fat available to the body is then the fat the body can form from carbohydrate, and this is relatively saturated (non-EFA) fat. Conversely, a high-fat diet is also in general harmful since the ordinary fats included in our diet are relatively deficient in EFA (butter, lard, dripping, meat-fat, margarine—though this last can be an important source of EFA depending upon the method of manufacture). What is required is to decrease the non-EFA fat in the diet and increase the EFA. There are pharmaceutical preparations available for this and there is a large use of vegetable seed oils (maize or corn oil, sunflower seed oil) in the United States. There is no great difficulty in taking 3 ounces (85 g.) of maize oil daily, which provides about 50 g. of linoleic acid and also vitamin E. Since pyridoxine (vitamin B_6) appears to be becoming deficient in our diets (Sinclair, 1958b) this must also be supplied (10 to 50 mg. daily).

It may cause surprise that as much as 50 g. of linoleic should be administered; 3 ounces (85 g.) of corn oil provides about 750 calories and might lead to obesity unless other fat and carbohydrate are reduced as is strongly desirable. There is evidence that if linoleic acid is ingested as neutral fat (triglyceride), which is the form in maize oil, it is rapidly oxidized in the body and only part is available for EFA-functions; this is true even in an animal that is suffering from deficiency of EFA. But if linoleic acid is given in the form of a lecithin (a phospholipid) then it may be absorbed as such and protected from rapid oxidation for energy purposes; it is probably as part of phospholipids that EFA play their most important functions. In this way quite small amounts of EFA may be sufficient to treat these diseases. A pharmaceutical preparation of lecithin rich in EFA is marketed in Germany; until more research is done—and research is urgently needed in the whole field of EFA—we cannot say what foodstuffs are good sources of lecithins containing EFA; eggs, for instance, vary according to the diet of the hen. So for the present we must rely mainly on vegetable seeds (nuts, whole-wheat bread) and their oils such as maize oil, and certain fish, such as herring.

CONCLUSION

This article has discussed advances in nutrition and dietetics with respect to fats. Unfortunately this is a subject in which the evidence is conflicting and therefore liable to lead to confusion. Our ignorance does not permit of clear guidance being given to the practitioner, the patient or the public.

Fats are very important in our diets. They are the most concentrated form of energy; they help to make the diet palatable and provide satiety; some of them are sources of the fat-soluble vitamins (A, D, E and K) and they help the absorption and utilization of these; they are the only sources in the diet of the essential fatty acids. But these nutrients (EFA) are only

provided by a few fats, and many other fats increase the need for EFA in the diet. Therefore there are harmful fats and beneficial fats. This is not a question of animal in contrast to vegetable fats, or of saturated in contrast to unsaturated fats. The processing of fats—and digestion in the rumen of cows and sheep can be regarded as processing—tends to convert the type of linoleic acid we need into geometrical and positional isomers that have no EFA function. These are long and empty words for the busy practitioner. Cod-liver oil and tung oil contain highly unsaturated fats, but the double bonds are wrongly distributed in the molecules for EFA activity. Cow's milk, particularly if dried and kept in air, is very inferior to human milk as a source of EFA. Many vegetable seed oils, but not olive oil, are very rich in EFA.

These oils are powerful in lowering serum cholesterol. But it is not proven that a high serum cholesterol leads to atheroma, and it certainly does not cause coronary thrombosis. No-one should advise the public to consume large quantities of vegetable seed oil, but the present evidence is sufficient to warn that too much fat in the diet is harmful if this fat is of non-EFA type. How much of what kind of fat we should eat is a matter of balance in the diet. The pint of milk that advertisements advise us to drink is an excellent food if EFA are supplied from some other source. We urgently need research to define the beneficial and harmful fats.

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ADVANCES IN ORTHOPÆDICS

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It is fair to say that there has been no dramatic discovery in orthopædic surgery during the last four years, but on the other hand there is a continual 'striving after truth' and progress is often made as much out of failure as from success.

SURGICAL IMPLANTS

In both accident, and so-called 'cold', orthopædic surgery the use of implants of various kinds has persisted but certain facts have been clarified. With the widespread use of plastics in industry it was only natural that the use of these compounds in surgery should have been tried, and this was brought well to the fore by the Judet Brothers (1950) when they introduced femoral-head replacement in the treatment of femoral-head fractures and chronic arthritis of the hip. Unfortunately, fracture and fragmentation of the prostheses commonly occurred, together with a certain amount of intolerance on the part of the host tissues with marked fibrous tissue reaction (fig. 1).

Similarly with nylon there is a phagocytic response which can result in bone destruction, and Scales (1956), in comparing polymethyl methacrylate, nylon and polythene implants, is of the opinion that 'the degree and type of cellular response is dependent on the abrasion-resistance of the implant'.

In turning to the metals it has long been recognized that corrosion and fatigue or stress fracture can occur in steel plates and screws attached to bone (fig. 2a). This may be the result of a process of rust formation, but in other cases electrolysis plays an important part (fig. 2b) and if two different metals or alloys of different chemical composition come into contact in the presence of the tissue fluids, which act as an aqueous electrolyte, a simple voltaic cell is set up. Thus it is essential that surgeons use stainless steel implants of uniform composition and identical specification in the body. To this end an attempt is now being made in both Britain and the United States to correlate research work and formulate standards.

There are two metals now in general use:—

(1) Austenitic stainless steel (E.N. 58 J British Standard Specification). This has basically an 18 per cent. chrome and 8 per cent. nickel content with 2 to 4 per cent. molybdenum, and is non-magnetic and corresponds to the American S.M.O. type 316.

(2) Chrome, cobalt, molybdenum alloys pioneered by Austenal's vitallium. This alloy is electrolytically inert and was used by Smith-Petersen in his final development of the mould arthroplasty operation. In a large personal series of these cases over the last twelve years, there has been no instance of corrosion or fragmentation of a cup or mould made of vitallium. This contrasts markedly with moulds made of ordinary stainless steel.

In this country certain items have been fabricated under the trade name 'vinertia', which has specifications identical with vitallium. More recently

titanium has shown itself to be inert, but at present the physical properties are such that it is not considered suitable for a full range of surgical implants.

OSTEOARTHRITIS OF THE HIP AND VASCULAR SUPPLY OF THE FEMORAL HEAD

Trueta and Harrison, using a special injection technique, worked out the vascular pattern of the head and neck of the adult femur, and subsequently Trueta (1957) described in detail the normal vascular anatomy of the human femoral head during growth. He describes five main phases:—at birth, infantile, intermediate, pre-adolescent, and adolescent when the adult stage of the circulation, with anastomosis between the three sources of blood supply, metaphysical, epiphysial and ligamentum teres, takes place. The vessels of the ligamentum teres do not contribute to the blood supply of the femoral head until after the age of eight or nine years; at this time the vessels of the metaphysis are arrested. These latter become active again at puberty. In old age free vascular communications are maintained in the femoral head and in cases of osteoarthritis they even demonstrated an increased blood supply. Lloyd-Roberts (1955) has also shown that in osteoarthritis the bone remains well vascularized and that avascular necrosis is only seen when fragments become detached as may result from cystic formation.

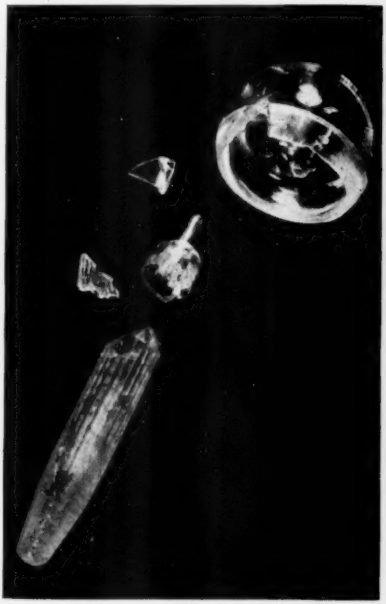


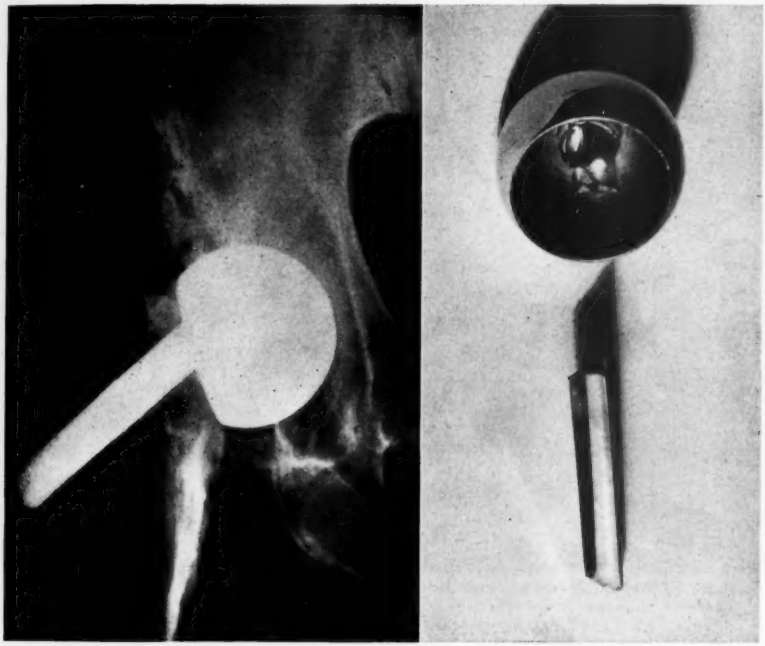
FIG. 1.—A fragmented Judet acrylic prosthesis.

Little, Pimm and Trueta (1958) made an electron microscope study of osteoarthritis of the hip concentrating upon the early changes in the hyaline articular cartilage. It was seen that the orientation of the collagen fibrils is different and that the ground substance is less, this being confirmed chemically by diminution in total polysaccharide in the arthritic cartilage. The site of earliest degenerative change is in the non-pressure areas of the joint, the articular cartilage being thickest over the weight-bearing areas; clearly the value of maintaining joint function as a means of nourishing the articular cartilage must be stressed in considering treatment, particularly in the early stages.

Nissen (1958) has performed the operation of horizontal forage at the subtrochanteric level of the femur in a number of early cases of osteo-

arthritis. The object of this procedure is to cut the main blood supply which runs upwards from the shaft into the base of the neck of the femur, and in this way he has successfully and dramatically relieved pain. Possibly this is the reason that McMurray's osteotomy also relieves pain, and it is clear that the relationship of femoral head and neck blood supply to the symptoms of pain in arthritis of the hip will require further study.

In the advanced case with severe pain, deformity or stiffness, surgical intervention is of value and may be carried out along one of four main



(a) (b)

FIG. 2.—(a) X-ray of broken metallic prosthesis—18 months after operation. (b) The stainless steel head as seen after removal.

lines: arthrodesis, arthroplasty, McMurray osteotomy, or pseudarthrosis of the Girdlestone or Batchelor type. Each method has its indications and the choice must be made on individual merits and requirements. In regard to arthroplasty, the acrylic or metallic femoral head replacement of the Judet type has too often fragmented and the trend is towards prostheses of the Austin-Moore (fig. 3) or Thompson type with intramedullary stems going down the femur. The vitallium mould (fig. 4) has produced a reasonable proportion of satisfactory results in recent five- to ten-year surveys (Aufranc, 1957; Denham and Law, 1957).

SLIPPED UPPER FEMORAL EPIPHYSIS

There is no doubt that many cases of slight adolescent coxa vara never present themselves for diagnosis or treatment, but a number of these may develop osteoarthritis at a relatively early age. Jackson Burrows (1957) reviewed one hundred cases of slipped upper femoral epiphysis and noted that in one-third of the cases treatment was delayed and that diagnostic

FIG. 3.—Austin-Moore prosthesis used in a patient with a metastatic deposit in the femoral neck. The patient was alive and well three years after operation.

FIG. 4.—A Smith-Petersen vitallium mould ten years after operation. Note absence of bone reaction.

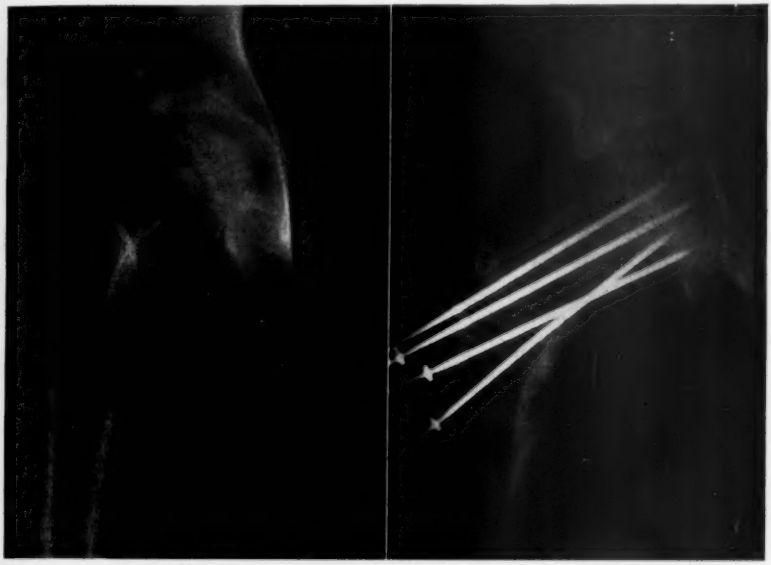
failure was the reason in 19 out of 34 cases. Boys are more commonly affected than girls, who usually present at a much younger age, 11 to 13, as opposed to 14 to 16 years. It is exceptional to find epiphysial slipping after the onset of menstruation. Injury as a relevant factor was seen in half the patients and was more common where the slipping was sudden as opposed to gradual. Endocrine defects were recognized in a quarter of the boys and nearly two-thirds of the girls.

In discussing the results of treatment in this series, Hall (1957) stresses the value of a firm gentle manipulation with medial rotation in reducing the displacement safely (fig. 5a) and noted that avascular necrosis did not occur in a single case subsequently treated with Moore's pins (fig. 5b), in contrast to an incidence of 37 per cent. when a Smith-Petersen nail was used. Where

a corrective cervical osteotomy had been performed the incidence of avascular necrosis was 38.1 per cent.

THE PAINFUL SHOULDER

Impressions may be fallacious, but it would certainly seem that patients



(a) (b)

FIG. 5.—(a) Slipping of the femoral epiphysis, with (b) reduction and fixation with Moore's pins.

with painful and/or frozen shoulders are becoming more common. In a series of 2,580 cases, Harmon (1958) groups the clinical diagnosis as follows:

Frozen shoulder (813); calcification of the shoulder cuff (609); supraspinatus tendinitis (887); biceps tendinitis (154); rupture of the long head of biceps (76); rupture of shoulder cuff (44); dislocation of the biceps tendon (7).

In cases of shoulder-cuff tendinitis, with or without calcification, treatment by injection with local anæsthetic and hydrocortisone suspension, followed by needling in conjunction with physical therapy, heat and rest proved effective in 80 per cent. of cases. In only 3 per cent. did symptoms persist so as to warrant surgery—resection of the acromion process and acromio-clavicular joint—and this was effective in 76.9 per cent. Deep x-ray therapy was not considered an effective line of treatment by this author, although experience in this country has shown it to be of some value.

The true frozen shoulder often goes through three definite phases: (1) 'freezing' of the joint, usually accompanied by acute pain; (2) a stationary phase with dull aching pain and no joint movement; (3) a final stage of resolution with slow return of joint function. In the first stage treatment

by heat, rest and salicylates is all that is indicated. Local hydrocortisone is not helpful as a rule. In phases 2 and 3 gentle manipulation under anæsthesia may well help treatment with active shoulder-mobilizing exercises and can be repeated as necessary. Where there are changes in the acromio-clavicular joint excision of the acromion process or the outer end of the clavicle may prove of real value, as the secondary pathological changes are thus eliminated and these certainly tend to aggravate the primary adhesive capsulitis and fibrosis. On the whole, in Britain local hydrocortisone has proved much more effective in the painful elbow (tennis elbow) type of lesion than in the painful shoulder.

SURGERY IN THE RHEUMATIC DISEASES

With the modern trend towards an ageing population and the great sociological problem of caring for these patients it is not surprising to find the orthopædic surgeon being called upon to relieve pain and deformity in rheumatoid and osteoarthritic joints as well as to restore enough function in these limbs to enable the patient to lead a relatively independent existence. The hip joint has already been mentioned in this respect, but progress has also been made in treating the hands, feet, knees and spine in such patients.

The characteristic deformity of the rheumatoid hand is well known, but it was left to Vaughan-Jackson (1948), and later Straube, to describe the reason for sudden loss of extensor power in the fingers, which occurs as the result of attrition rupture of the extensor communis digitorum on a rough area on the head of the arthritic ulna, which penetrates the sheath and wears through the tendon. The deformity is not therefore caused by rheumatoid degeneration, and repair can be effected by tendon grafting or sometimes suture. More recently similar ruptures have been noted in flexor tendons. In the main the deformity in the rheumatoid hand is due not only to joint changes but also very considerably to fibrosis and contracture of the joint capsules and ligaments and the intrinsic muscles, with displacement of the extensor tendons. Bunnell (1955) stressed the part played by muscle imbalance in determining the deformity and, of course, in the early stages a great deal can be achieved by splintage and exercises to prevent atrophy and contracture. The spring cock-up splint and reverse knuckle-bender are useful 'live' splints for this purpose. In the later case the ulnar deviation can be corrected by resecting the heads of the metacarpals and freeing the metacarpo-phalangeal joints by tenotomizing the transverse aponeurosis and lateral ligaments. The extensor tendon is freed and re-aligned on the radial side of the joint and in this way considerable reduction in deformity and improvement in function can be achieved.

In the cases of very deformed toes, with gross clawing, contracture and painful pressure points, amputation of all the digits provides great relief from symptoms and marked improvement in function. The footwear requires adjustment with toe blocks, but this procedure may well enable crippled patients to walk comfortably again.

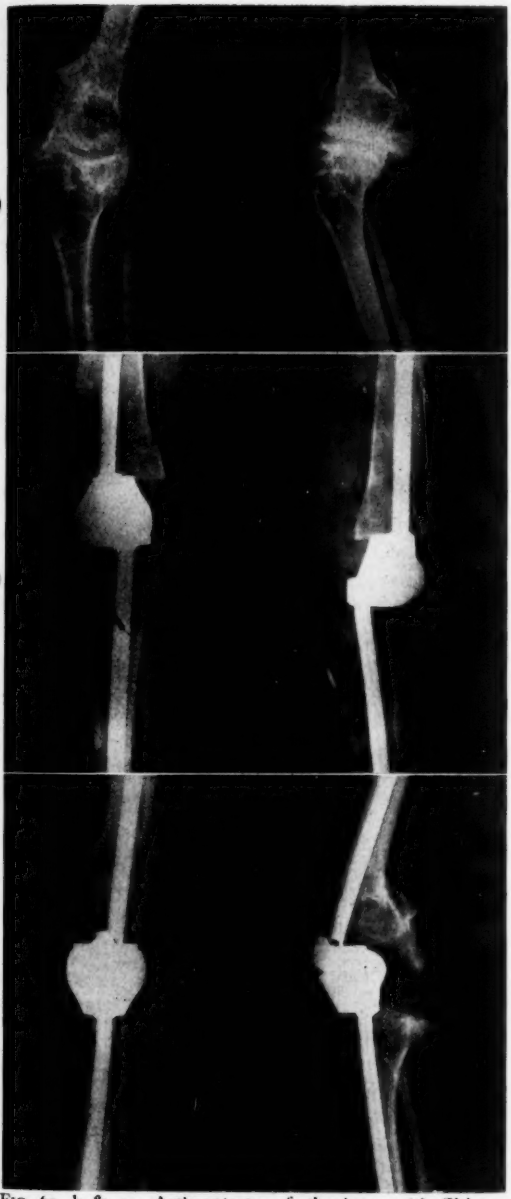


FIG. 6a, b & c.—Arthroplasty of the knee with Shiers hinge. The break in the prosthesis occurred after two years and was treated successfully by replacement.

The problem of painful, stiff knee joints, particularly when bilateral and accompanied by similar changes in hips and ankles, is an extremely difficult one. A sound arthrodesis provides painless stability, but in patients with multiple joint involvement in both upper and lower limbs, it is extremely difficult for them to attain the upright position unaided. Much work has been done on the problem of knee arthroplasty, but an adequate range of movement combined with stability has been difficult to achieve. Aufranc and Jones (1958) use a vitallium mould over the lower end of the femur, slightly deepening the tibial articular surfaces, and have obtained a flexion range varying from fifteen to ninety degrees with alleviation of pain and stability in half their cases. Shiers (1954) introduced a metallic hinge with femoral and tibial intramedullary stem attachments. This certainly pro-

vides stability and movement up to about ninety degrees, but there has been the problem of metal fatigue which has resulted in the prosthesis breaking. In a series of twenty-five cases thus treated by Shiers and Law, twelve patients were quite satisfactory three years after operation (fig. 6a, b, c).

In osteoarthritis of the knee principally affecting the inner joint compartment with valgus deformity, MacIntosh (1958) has used a tibial plateau prosthesis, which restores the height of the tibial plateau and relieves pain and deformity without loss of stability. Collateral and cruciate ligaments are left intact and in a small series of cases the results of this hemi-arthroplasty of the knee certainly seemed encouraging.

In rheumatoid arthritis and ankylosing spondylitis the correction of severe rigid kyphosis by spinal osteotomy in the lumbar region has enabled dramatic improvement in the posture of very deformed individuals. Recently, I have adapted the operation to the cervical region with the object of relieving the flexion and rotation deformity and also preventing atlanto-axial subluxation which occurs in these cases more often than has formerly been realized (Law, 1958).

SCOLIOSIS

Many orthopædic surgeons are interested in this difficult subject. James (1957, 1958) in particular has made detailed studies of curve patterns in paralytic and other types of scoliosis. He has also described two types of structural scoliosis seen in infants: (a) resolving structural scoliosis which usually shows a left-sided thoracic curve with a strong tendency to spontaneous disappearance, and (b) infantile idiopathic scoliosis which is also usually a left-sided thoracic curve, occurring during the first three years of life and which is rapidly progressive. This is quite distinctive from scoliosis due to congenital defects and may require surgical treatment at a fairly early age.

Roaf (1958) stresses the part played by rotation in the establishment of scoliosis, pointing out that if vertebræ are fitted together in an abnormal rotatory relationship scoliotic deformity can be reproduced experimentally without lateral flexion. He also postulates a number of secondary deforming factors which tend to increase the deformity, which is really a lordosis rather than a lateral flexion. These include the pull of the longitudinal and transverse fibres of the erector spinæ, gravity, the distorted rib cage and the fact that upper and lower vertebral body surfaces are not parallel.

Treatment of scoliosis is still based on exercises for weakened muscle groups and prevention of further deformity by supports such as plaster and plastic jackets or braces of the Fischer, Blount, or Milwaukee types. Correction of the deformity is usually attempted by employing a Risser, or a distraction, jacket followed by spinal fusion for the whole of the primary curve, which is the region where rotation persists on forward flexion. Perhaps in the future more determined attempts should be made to effect derotation.

FRACTURE OF THE OS CALCIS

These fractures have always presented a difficult problem in treatment, with poor results being all too common. Lindsay and Dewar (1958) examined 390 case-histories of old fractures of the os calcis and carried out a detailed personal follow-up study on all those involving the sub-astragaloid joint (70 per cent.). They use a simple classification based on the degree of deformity of the os calcis: (a) moderate, (b) severe, (c) fracture involving the sub-astragaloid joint without displacement. The methods of treatment included the Hippocratic tensor bandaging and elevation, plaster immobilization, manipulative moulding, disimpaction, traction and sub-astragaloid arthrodesis carried out either immediately or shortly after the injury was incurred. In 82 patients treated conservatively 55 (79 per cent.) remained at heavy work and in 70 patients treated by arthrodesis 31 (49 per cent.) returned to heavy labour. Where deformity was severe the results of conservative treatment unexpectedly proved to be better than those obtained by surgery. Where deformity was moderate the good results of conservative and surgical treatment approximate. In the cases treated conservatively attempts at closed reduction appear to be of doubtful value and pin-track sepsis occurred in 11 per cent. of cases.

There is no doubt that many attempts at reduction in fractures of the os calcis are unsuccessful, but it is interesting that the percentage of good clinical results is not increased even when such attempts are successful. Pain in the hind-foot after fracture of the os calcis has too often been attributed to the sub-astragaloid joint. Both heel and lateral malleolar pain seem to originate in soft tissues and are not relieved by sub-astragaloid arthrodesis. Mid-tarsal joint pain is not usually disabling and ankle-joint pain resulting from osteoarthritic changes is more common than formerly realized, the articular cartilage possibly being damaged in the violence at the original accident. The common lateral malleolar pain does not appear to be due to impingement of the lateral malleolus on the thickened os calcis and is probably more in the nature of a chronic ligamentous strain. It would appear that a more simple approach to the os calcis fracture may give better functional results, and this certainly is the modern trend.

FRACTURE OF THE TIBIA AND FIBULA

In these days of speedy mechanical transport and congested roads these fractures are extremely common. The problem in treatment is that of closed or open reduction. In children, closed manipulation and plaster immobilization is undoubtedly the method of choice and is more universally accepted. In adults, however, there is a greater tendency to open reduction and internal fixation on the Continent and in North America than in Britain. Where the fracture is closed and stable there seems to be no excuse for open reduction and internal fixation. The danger of complications—infection and ischæmia from periosteal stripping—is too great and union occurs more rapidly: 7·7 months as compared with 9 months in a series described by Wade and Camp-

bell (1958). An intact fibula is always associated with quicker healing.

In unstable fractures internal fixation may be required on some occasions but by no means routinely. Sharp unstable bone fragments likely to damage the soft tissues may have to be controlled in this way, even in open fractures, but soft-tissue and skin closure are essential over the fracture site and only the minimum foreign-body fixation should be used in conjunction with external fixation by plaster. Screws and intramedullary nails such as those of Lottes and Rush appear to be tolerated better than plates, and the use of Parham bands and encircling wires for oblique spiral fragments seems to have become more popular recently. The presence of infection or contamination must preclude nailing. In Wade and Campbell's report the incidence of non-union in closed fractures was 18 per cent. in cases treated by open reduction and nil in those treated in a closed manner. In the open fractures without internal fixation the incidence was 15 per cent. as opposed to 11 per cent. where internal fixation was used.

CONCLUSION

There is no doubt that in the large field covered by the orthopædic surgeon, both as regards trauma and bone and joint disease, in addition to soft-tissue lesions of structures such as tendons and peripheral nerves, there is still plenty of room for further advances in the future.

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ADVANCES IN NEUROSURGERY

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So vast is the scope of neurosurgery today that I have restricted this review to four aspects of the subject: hydrocephalus, intracranial hæmorrhage, epilepsy, and stereotactic surgery.

HYDROCEPHALUS

For many years hydrocephalus in infants has provided scope for the ingenuity of neurosurgeons in devising operations for its relief. The use of dyes injected into the ventricles and of air-encephalography—both devised by Dandy—is necessary for the detection of the cause of the obstruction to the flow of cerebrospinal fluid (C.S.F.), and to demonstrate the degree of ventricular dilatation. A common cause is maldevelopment or atresia of the aqueduct of Sylvius. In older patients narrowing or stenosis of the aqueduct may occur as a result of gliosis. Other congenital malformations in the C.S.F. pathway may occur at different points; the Arnold-Chiari malformation, with which there is usually spina bifida, affects structures in the posterior cranial fossa. The lower portions of the cerebellar lobes and the medulla come to occupy the foramen magnum and uppermost part of the cervical spinal canal. The upper few segments of the cervical cord are consequently to be found at a lower level than normal. Adhesions form between the abnormally crowded structures within the foramen magnum and the enclosing membranes; the malformation obstructs the flow of C.S.F. from the fourth ventricle, through the subarachnoid spaces to the basal cisterns. Adhesive occlusion with fibrosis of the pia-arachnoid is a common cause of hydrocephalus, and may result from blood escaping into the meninges in a birth injury and from meningitis. Intracranial tumours occasionally occur in infants and enlargement of the head is commonly the first manifestation. A papilloma of the choroid plexus not only produces a mass by virtue of its growth, but often causes enlargement of the ventricles in addition. The head may enlarge rapidly in infants as a result of fluid collections between the dura mater and the arachnoid over the surface of the cerebral hemispheres; the fluid may be blood, forming a subdural hæmatoma, or may be a yellow turbid transudation complicating acute meningitis.

The first step in dealing with an infant with enlargement of the head is accurate diagnosis. The history may indicate the likelihood of the condition being due to a subdural hæmatoma or effusion. The urgency of the condition and the frailty of the patient may preclude drastic measures, but the diagnosis can be ascertained by aspiration of the subdural space on both sides of the head with a sharp needle inserted through the coronal suture. If a sub-

dural collection of fluid is detected, it can be treated by repeated aspiration, though when the infant is stronger more drastic surgical measures may be needed to cure it. In other cases the tests mentioned earlier will be necessary to demonstrate as precisely as possible the situation and the nature of the block to the flow of C.S.F. In some cases a tumour (e.g. papilloma of the choroid plexus) will be unexpectedly revealed, and for this reason x-ray examination with air is essential. In cases of obstruction of the aqueduct, an alternative route of escape for the C.S.F. must be provided. An opening, for instance, can be made in the anterior wall or the floor of the third ventricle; these structures are rendered very thin by the distension of the third ventricle, and consequently the operation is not so difficult or dangerous as it may sound. Fluid then escapes into the basal and chiasmal cisterns and thence circulates over the cortex. Another type of operation is Torkildsen's ventriculo-cisternostomy. One end of a piece of narrow-bore, non-irritating tubing, such as polythene or silicone rubber, is passed into the posterior part of the lateral ventricle through a suitably placed burr-hole; the other end of the tubing is placed within the cisterna magna, the intervening portion being buried under the suboccipital muscles. This operation has proved a valuable palliative measure in cases of slowly growing irremovable tumour so placed as to cause hydrocephalus. Obstruction due to Arnold-Chiari malformation can be relieved by a posterior fossa decompression.

The treatment of hydrocephalus due to meningeal adhesions is more difficult. Dandy excised the choroid plexuses of the lateral ventricles, thus diminishing the quantity of C.S.F. secreted. Subsequently, Putnam and Scarff destroyed the plexuses by endoscopic coagulation. Unfortunately these operations rarely destroy all the secreting tissue in the lateral ventricles, and leave intact that of the third and fourth ventricles. Attempts to drain C.S.F. into other tissues have been unsuccessful, but the principle has been applied in other ways. In one—arachnoperitoneal anastomosis—a thin non-irritating tube is implanted through the posterior abdominal wall, so that one end lies within the C.S.F. space of the lumbar sac, and the other end lies in the peritoneal cavity. Although the tube is liable to become blocked by fibrinous exudate, or to be sealed off by peritoneal adhesions, necessitating revision, this operation has had a measure of success; it has a low mortality and no unpleasant consequences. Arachno-ureteric anastomosis is an alternative operation. One end of a tube is implanted in the lumbar theca, and the other end is passed into the upper end of the ureter on one side, after the kidney has been removed; C.S.F. is thus excreted into the bladder, and is voided. This operation undoubtedly succeeds in relieving communicating hydrocephalus, but it has considerable disadvantages. It demands the sacrifice of one kidney, and therefore, before such an operation can be performed, the presence of two functioning kidneys must be ascertained. The continual loss of C.S.F. from the body means a loss of water and of electrolytes, and it is usual to prescribe 2 grammes of sodium

chloride a day for an infant. In the event of an acute pyrexial illness, dehydration and electrolyte disturbance can create a major complication. A urinary infection will easily extend to an acute meningitis. Another operation, simple to perform, but open to similar grave risks of meningitis is the implantation of a tube so that one end rests in the temporal horn of the ventricle, and the other in the mastoid antrum. More recently attempts have been made to devise a minute plastic valve incorporated in a length of tubing, so that C.S.F. can be shunted from the ventricle into a large vein in the neck. Such a method mimics the natural absorptive mechanism, but difficulties such as thrombosis have not yet been fully overcome.

It must be admitted that the surgical treatment of infantile hydrocephalus is still unrewarding in many cases. It is likely that the lack of success of short-circuiting operations is often due to the failure of the cortical subarachnoid spaces to open up when the C.S.F. is redirected into them. In other cases, failures are due to adhesions forming after the operation. The complications of the anastomosing operations have already been described. It is common practice therefore not to operate on cases in which ventriculography reveals grossly dilated ventricles; moreover, the brain is so damaged by gross hydrocephalus that it cannot develop into a normal organ and a mentally defective child, even an imbecile, is the final result.

INTRACRANIAL HÆMORRHAGE

In recent years, neurosurgeons have taken an increasing part in the treatment of spontaneous intracranial hæmorrhage. Analysis of post-mortem material has shown that in about one-half, hæmorrhage has been due to hypertension and its attendant vascular degeneration; in nearly one-quarter the hæmorrhage came from a ruptured aneurysm or a congenital vascular malformation (hamartoma) in the proportion of roughly five to one. The increasing use of cerebral angiography has also provided evidence that aneurysms are much commoner than was formerly thought to be the case. Further, the notion that aneurysmal rupture is a disease of young persons is incorrect; about half the patients are over the age of 50 years. Aneurysm and hamartoma, of course, give rise to symptoms other than hæmorrhage, which lead to the use of angiography for accurate diagnosis. Hæmorrhage may be more or less entirely on the surface of the brain—usually the basal surface—or the position of the aneurysm may be such that the rupture occurs into the brain substance, forming an intracerebral hæmatoma; this happens in at least one-quarter of the cases. If hæmorrhage is severe, the immediate brain damage is lethal of itself, and the patient dies within forty-eight hours. Thereafter the chances of recovery improve considerably with each day's survival, but relapse is likely to occur for three main reasons. Further brain damage may occur from impairment of its circulation, due to the development of spasm of the main cerebral arterial tree which carries the aneurysm; this spasm gradually subsides after a week or so, but its consequent effect may be to produce, say, a hemiplegia, or it may even

prove fatal. In other cases relapse may be due to the cumulative compressing effect of the hæmatoma, whether intracerebral or subdural. Thirdly, the aneurysm may bleed again; this is particularly likely in the few weeks following the first rupture, or it may be deferred for months or years. Estimates of the mortality of ruptured aneurysm (treated conservatively) can only be approximate as they are restricted to hospital admissions; at least one-third of the patients die during the hospital admission necessitated by the first hæmorrhage, and about one-quarter of the survivors die of a recurrent hæmorrhage after they have been discharged from hospital.

The role of surgery in a case of spontaneous intracranial hæmorrhage is to save the patient's life, to promote as full recovery of function as possible, and to prevent a further hæmorrhage. The surgeon cannot help in the case of the massive lesion which kills in twenty-four to forty-eight hours, but in the survivors, hæmatomas can be evacuated, averting death by cerebral compression, diminishing the severity of the hemiparesis and speeding the rate of recovery, and often the aneurysm can be successfully obliterated, thus preventing another hæmorrhage. Angiography is essential in order to demonstrate the aneurysm (or hamartoma), revealing its vessel of origin, its precise situation and orientation and its size. Angiography also demonstrates the degree and extent of vasospasm, and it can be used to show to what extent the circulation in one hemisphere can be maintained through the circle of Willis when the internal carotid artery on that side is occluded; ligation of the parent carotid stem may be the only surgical treatment feasible.

An important question immediately arises at this stage. When should angiography be carried out? This rests on the surgical decision as to when an operation should be undertaken—if at all. Some neurosurgeons believe that operation should be deferred until any vasospasm which may be present has subsided, and an arbitrary period of three weeks after the hæmorrhage is allowed to elapse. But it is well recognized that further hæmorrhage may occur within this period and be promptly fatal. Compression by hæmatoma may be mistaken for the effect of vasospasm, and prove fatal within this period. On the other hand, too early operation in a very ill patient may prove fatal. The tendency of most neurosurgeons in this country is to wait at least twenty-four to forty-eight hours, and in a deeply comatose patient to wait for spontaneous improvement; thus, operation is usually undertaken at about the end of the first week. Angiography should be carried out as soon as possible after the first day or so. Experience has shown that there is virtually no risk of precipitating further hæmorrhage, and early knowledge of the information which can be derived only from angiography is of the greatest value in planning treatment.

The surgical treatment of intracranial aneurysms and hamartomas, whether giving rise to hæmorrhage or to other symptoms and signs, has been well nigh revolutionized by the introduction of induced hypotension and of hypothermia during the operation. The controlled reduction of

blood pressure facilitates a bloodless field, enabling the surgeon to see clearly the aneurysmal sac, or vascular malformation. The reduction of the pressure of blood within the sac enables the delicate dissection around it to be undertaken with less risk of its rupture; if rupture occurs, hæmorrhage is not so profuse that mechanical suction fails to keep the field clear. But hypotension of this degree carries the risk of anoxic damage to the brain, the heart and other organs, with attendant sequelæ. By reducing the temperature of the body sufficiently, the metabolism of the cells is so reduced that the oxygen supply during hypotension is still adequate; hypothermia renders hypotension safe. A rectal temperatue of 30° C. is employed; at this level the blood pressure commonly falls to about 80 mm. Hg, and, if necessary, it can be further lowered by hypotensive drugs. An alternative or additional method is to obstruct temporarily both common carotid arteries if the aneurysm is torn during dissection, thus rendering the escape of blood a mere trickle. The exposed aneurysm is obliterated by small metal clips, or its neck is ligated. Occasionally the aneurysm cannot thus be dealt with, as it may give off vital arteries from its walls. Should this be the case, it may be surrounded by muscle or wisps of cotton-wool or by a plastic, in the hope that these will form a firm coating of scar tissue; carotid ligation is sometimes preferred. At the time of the craniotomy a hæmatoma may be encountered and evacuated and in some cases this will be of paramount importance.

EPILEPSY

Successful surgical treatment of epilepsy has been a development of the second quarter of this century, and stems largely from the activities of Penfield, who began to study brain scars and their relation to traumatic epilepsy in 1921. The basis of operation depends upon the assumption that epilepsy is the manifestation of a sudden spontaneous 'discharge' of activity by a group of nerve cells: the so-called 'epileptic focus'. This discharge may remain limited to that group of neurones, or it may spread like a chain reaction to others. The pattern of the epileptic seizure as noted by the observer, and perhaps by the sufferer, will depend upon the functions of the group of cells which discharge, and those which may be secondarily affected. The subject may be conscious throughout the attack and may remember precisely the order and nature of the events. He may recall only the early events; or the fit may render him immediately unconscious and he will have no knowledge of what has happened. Thus, it is of prime importance to obtain the fullest accurate chronological details of the seizure, from observer and subject, as these may provide precise evidence as to where the 'epileptic focus' is situated. Clinical classifications of epilepsy are based upon analyses of these patterns. The investigation of epilepsy has been greatly aided by the electroencephalograph (E.E.G.), which demonstrates abnormalities of the frequency and amplitude (voltage) of the fluctuations in the minute changes of electrical potentials, recorded simultaneously from a variety of

points on the scalp. These abnormalities may be present for short bursts or for long periods, even when no actual clinical attack is taking place. The abnormalities may be diffuse and bilateral, or may be more marked in a particular area; or the record may be normal except in one particular region. Much has been done to correlate the types of E.E.G. abnormalities with the clinical type of seizure, and the E.E.G. may offer valuable help in localizing the focus, or it may make it clear that there is more than one focus, or that the cerebral cortex is simultaneously affected on both sides as from a deep and centrally situated disturbance.

In recent years particular attention has been paid to a form of epilepsy termed psychomotor, in which convulsive (motor) activity may be minimal, e.g. chewing movements or slight twitching of the mouth, but in which there is a transient disturbance of behaviour which can be explained on a basis of some disorder of the psyche. This may be slight, e.g. groping movements of the hands suggesting the patient is seeking something; or of a more severe degree such as undressing or wandering away. Occasionally the behaviour disorder may last a considerable time, may be of an antisocial kind and may bring the patient into conflict with the police; there may be violence if the patient is constrained. The patient has no recollection of his abnormal behaviour although he may recall subjective abnormalities at the beginning of the fit; such as hallucinations of special senses, or dream-like states. In some of these patients repeated attacks may lead to temporary psychosis. There is much evidence, part clinical, part E.E.G., and part the result of operation, that this type of epilepsy can arise in the temporal lobe and the loose term 'temporal lobe epilepsy' is often used. Operations have shown that quite small and unsuspected tumours and malformations can be the cause, as well as gliosis due to a birth injury.

If the concept of an 'epileptic focus' is correct, and if the focus is accessible and its removal will not leave the patient handicapped by any serious neurological deficit, then operative removal of the portion of brain responsible for the epileptic discharge is logical. Consequently, the indications for operation are: the failure of anticonvulsant drugs to stop the fits or to reduce their frequency to a level compatible with social and economic requirements; the ability to postulate a single focus of epileptic discharge which is surgically accessible; the assurance that operation carries little danger to life and will not create another disability; the likelihood in some cases that the 'cause' is a tumour. Clearly each case is judged on its merits and the several criteria will not carry equal value in all cases; a decision cannot be made without extensive radiological and E.E.G. investigations.

At operation, the surgeon seeks to identify an area of brain in which the epileptic process is believed to originate. He may do this by applying the electrode of a stimulator to the cortex, systematically working over the field, the operation being performed under a local anæsthetic; in the appropriate area the stimulus may evoke a typical fit, or the aura which the patient will recognize and report upon. The sterile electrodes of an E.E.G. apparatus

can be applied to the brain (electrocorticography, E.Co.G.) and the record examined in the theatre. By repeated examination with differing settings of the electrodes, it may be possible to localize a piece of brain which persistently shows the characteristics of an epileptic focus. When uncertainty persists, the intravenous injection of certain drugs or stimulation of the brain electrically may demonstrate clearly a local abnormality of the E.Co.G. If an obvious lesion such as a tumour or scar is present, its removal does not necessarily remove the piece of epileptic brain; the focus usually lies alongside the lesion and the search for the focus must still be made. The focus having been identified, it is excised together with any lesion which may be present. This must be done with as little damage as possible to the blood supply of the neighbouring cortex, to avoid the risk of leaving ischæmic tissue which might be the origin of fresh epilepsy. In some cases the resection brings the surgeon close to areas of cortex which if damaged would lead to serious defect: e.g. dysphasia. For this reason it may be necessary to identify the normal function of that cortex by electrical stimulation. When the resection has been completed, the surgeon repeats his tests, by stimulation or by E.Co.G., to confirm that all the epileptic tissue has been removed. In order to achieve this, it is often necessary to extend the resection.

The results of the surgical treatment of epilepsy still leave much to be desired. Many patients are seen, few are selected as suitable for surgery. Of these few, the general picture from many sources is that cure, or reduction of fits to perhaps one or two a year, with resumption of employment, is obtained in about half. In another twenty-five per cent. there is distinct improvement. These results should be judged against the background of social and economic disability which is the lot of some epileptics. Rarely is a patient made worse by operation, and the mortality is fortunately low; about 1 to 2 per cent. The risk of lack of success may well be considered justifiable if there is a reasonable prospect of amelioration, particularly in those patients who are subject to behaviour disorder which entails their possible admission to a mental hospital or epileptic institution. It is usual to continue the administration of drugs and, if fits do not recur, gradually to diminish the dose. The study of epilepsy by clinical, E.E.G. and operative methods is a fascinating one, for each patient provides problems in neurophysiology.

The operative failures have stimulated research in advanced techniques of E.E.G. whereby use is made of indwelling electrodes inserted through small burr-holes in the skull. These may be placed over the surface of the brain, or as very fine insulated wires deep in its substance; they remain *in situ* for some days so that repeated records can be obtained. The results of such studies may show that the classical concept of the 'epileptic focus' will need revision, and that failure to respond to operation may be due to the presence of secondary foci, or of 'epileptic systems'. It is hoped that these studies will shed light upon the causation of those seizures in which

the discharge is perhaps generated in deep structures. Whether this will lead to further scope for operation is conjectural.

STEREOTACTIC SURGERY

In his research on neuro-anatomy and physiology, Horsley encountered the need for a method by which a small lesion could be made in a selected area deep in the brain, while inflicting negligible damage upon overlying structures. His co-worker, Clarke, invented a device which has become known as the Horsley-Clarke stereotaxic apparatus. It is still widely used in research laboratories: a fine wire electrode can be introduced into the brain through an appropriately placed hole in the skull, in a position and to a depth determined by measurements taken from an atlas of the brain of the animal in use. Nerve cells can be stimulated or destroyed, or the electrode can form a lead for recording the E.E.G. Necropsy can demonstrate precisely where the end of the wire was situated. Increasing knowledge of the connexions and functions of the basal ganglia and of the brain stem has revealed the possibility of relieving certain disabling symptoms by the surgical interruption of appropriate neural pathways. Division of these pathways by orthodox craniotomy has often proved as unsatisfactory in man as in the experimental animal, nor is it possible in many cases to make a small lesion with any assured success by 'free-hand' methods. The application of the experimenter's stereotactic technique has seemed to possess obvious advantages.

Stereotaxis has been used to introduce radioactive materials for therapeutic purposes into deeply situated tumours, which by reason of their situation are surgically irremovable. It has been used to make small lesions deep in the frontal lobes or in the thalamus, as an alternative to leucotomy for certain mental illnesses. The division of the pathways conducting painful sensation is desirable for certain cases of intractable pain. Cordotomy—division of the spino-thalamic tracts in the spinal cord—is a well-accepted operation; but in some cases it may be desirable to interrupt the pathways at a much higher level, nearer to the thalamus. Stereotaxis has been used successfully for this. Tremor and the muscular rigidity of Parkinsonism, chorea and athetosis, may cause profound disability to the sufferer, even though there be no paralysis of muscles. Many major surgical operations have been devised to afford relief; they have mostly failed, or else have given relief only in proportion to the degree of muscular paralysis caused by the surgical lesion. In the experience of some surgeons lesions placed in the globus pallidus or thalamus have proved helpful in about three-quarters of their cases. The most appropriate situation for the lesion is still a matter of opinion, and further time is necessary to assess results and to obtain necropsy material so that the precise extent and situation of the damaged area can be related to the type of involuntary movement, to the disease process, and to the degree of relief.

One of the limitations of stereotactic brain surgery is dictated by the variation in size of human brains, and in the distances within the brain of

various structures. Thus the distance between the anterior and posterior extremities of the third ventricle may vary by many millimetres from person to person. Likewise there is variation between the landmarks of the skull, and the location within it of a structure such as the pineal body which is often calcified and therefore identifiable in an x-ray. These difficulties render the application of stereotaxis in man more complicated than in the experimental animal. Various models of stereotactic apparatus for human use have been devised, though the principles involved are similar. The apparatus consists essentially of two parts:

One is a rigid metal frame which can be attached securely to the skull, usually at three or four points by small pegs or screws penetrating the outer table through small scalp incisions. To this framework can be fitted an adjustable arm or holder, which carries the electrode or instrument for making the lesion. This is usually in the form of a rigid wire or hollow needle, which is advanced into the brain through a small burr-hole, in the appropriate direction and to the desired depth. On the skull frame and on the adjustable arm are a series of measuring scales, linear or angular, whereby, given three dimensions related to fixed base lines or axes on the frame in horizontal, vertical and lateral directions, the lesion-maker can be directed to the chosen site. In practice, the frame is attached to the skull, the ventricles are filled with air (as in an encephalogram) and x-rays are taken. These will demonstrate the position of certain identifiable structures in the patient's brain—for instance the boundaries of the third ventricle—and also the metal frame. By calculation, with corrections to allow for the distortion due to the distance between the ventricle and the film and the diverging rays of the x-ray beam, measurements in three dimensions can relate the ventricle to the metal frame. From an accurate atlas of brain sections, one can measure the distances in these planes from the third ventricle to the anatomical structure it is desired to damage. These two sets of measurements are combined; the needle-holder is applied to the frame and so adjusted, using the calibrations on the instrument, that the needle when introduced into the brain to the calculated depth, will come to rest with its tip in the predetermined anatomical situation.

A matter which is still undecided is the best method of inflicting damage. It must be completely under control, so that the size of the resultant lesion is not conjectural or a matter of chance. It must not be liable to provoke hæmorrhage, or to thrombose vessels supplying distant parts of the brain. It must not cause the damaged brain to adhere to the needle and lead to further trauma during the removal of the needle. Lesions have been made by injecting small quantities of alcohol, by electrolysis (as used by Horsley), by surgical endothermy, and by rotating a snare and thus cutting through the tissues. Some of these methods are more suitable than others according to the desired size of the lesion.

Although stereotactic surgery seems a complicated procedure, and is time-consuming, and though the making of lesions deep in the brain by a method of measurement is foreign to a surgeon's training, in skilled and experienced hands it carries a low mortality. It is likely to have an expanding field of application in treatment and perhaps in investigation.

ADVANCES IN PREVENTIVE MEDICINE

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A REVIEW of achievements in preventive medicine must of necessity be broadly based; it should draw attention not only to 'traditional' successes in the control of infectious disease but also to less spectacular advances toward the prevention of the non-infectious and particularly of the 'new' diseases. As the prevention of infectious disease has been the subject of a recent article in this series (Parish, 1957), this review will deal with the latter subject.

THE BACKGROUND

In the complex of interrelated 'causes' of disease a variety of preventive measures is possible. Some are immediately successful, virtually eliminating the disease in a year or so, others contribute only a minute amount and give results only over long periods of time. Changes in the patterns of work, leisure or diet, standards of living and sophistication, the organization of medical care and research, are in this latter category. Their effect is general and is to be seen more, for example, in declining infant death rates and in increasing expectation of life and health than in the disappearance of particular diseases. It is unlikely that these social changes can rival in their impact the great triumphs over such diseases as smallpox and diphtheria. As our medical problems become more complex the likelihood of a 'break through' recedes and most of our recent advances are minor successes in an increasingly difficult struggle. Assisting these advances, however, and perhaps even to be counted among them are the changing attitudes of medical men, changes in social policy and changes in methods of medical research.

ATTITUDE OF DOCTORS

Preventive medicine is not a specialty in the same way as cardiac surgery or dermatology, and most clinicians are involved in its application. Because of the inevitable emphasis in medicine today upon the diagnosis and cure of existing disease, however, some doctors are still reluctant to admit their preventive role and are inclined to regard their responsibilities as going no further than the patient. Such a position is becoming difficult to maintain in the face of the rapid increase in our understanding of genetic, social, economic and other environmental factors in the production of disease. It is difficult to avoid the conclusion that all doctors have wide responsibilities for preventive action in eugenics, social and economic policy and health education, as well as in research and environmental control. A more general acceptance of these responsibilities and implications is an important advance in preventive medicine.

SOCIAL POLICY

But before the new and broader understanding of 'causes' can direct social policy in anything but the vaguest manner, far more facts about the interaction of disease and society must be known. Much post-war social legislation was based on little more than guesswork about the social factors which are related to disease. Yet in spite of the guesswork there seems no doubt about the usefulness of some of these changes in paving the way for preventive medicine. Social policy on housing, pensions, insurance and nutrition are examples. But some changes may have had a more direct effect: for example, the separation of cash payments from medical care may well prove to have been one of the most important ways to help the family doctor in his preventive work.

The health visitor particularly may be finding a new place in the preventive medical services. Changes in her role have been the subject of a working party (Inquiry into Health Visiting, 1956) and many articles (e.g. Rezler, 1957; Backett *et al.*, 1957). A further stimulus to change has come from experiments in collaboration between services, such as that at Oxford (under the medical officer of health).

Preventive medicine is sometimes seen also as a by-product of economic policy: for example, the recent recommendations to employ the elderly beyond retiring age (Report, 1954) might ultimately lead to an improvement in their mental and perhaps physical health (Anderson and Cowan, 1956). Or again, the rising cost of hospital beds has been an important stimulus to the development of domiciliary services designed for the prevention of disability (e.g. Adams *et al.*, 1957).

NEW TECHNIQUES OF STUDY—EPIDEMIOLOGY

Among the more important threats to our health—such as peptic ulcer, lung cancer, coronary heart disease, bronchitis, accidents, and the diseases of radiation—only peptic ulcer and some accidents respond well enough to treatment to afford workers in curative medicine any real satisfaction. Mortality from the others is dramatically high (Registrar General, 1957; General Register Office, 1957; Thomson, 1957). Clearly they must be prevented if they are not to become as serious as the major epidemics of the past. Fortunately, recent epidemiological studies have demonstrated beyond doubt that they could be prevented or at least kept in check. Proof rests upon the sure description of social patterns in their occurrence and their changing incidence in time. It means that amongst other predisposing factors, the environment is at fault. But this is not always the environment which we are accustomed to manipulate as a public health measure; increasingly it is the intimate *social* environment with its emphasis upon family customs and habits, diet, leisure activities and the like. These demonstrations are themselves considerable steps towards prevention. Techniques used in these studies have now become the principal and characteristic tools of preventive medicine research. The widespread and increasing use

of epidemiological techniques in this way is perhaps the most important recent advance in preventive medicine, although it is the least spectacular.

Epidemiology points to causes by describing the characteristics of vulnerable groups in the population. Such a description is the essential first step towards prevention. The field survey, the cohort study and the prospective study are refinements used increasingly in these descriptions.

The field survey is a technique whereby the illness experienced by a whole population can be studied. Using sampling and other methods, which owe much to the academic psychologists such as Spearman and Burt, workers studying pneumoconiosis in mine workers (Cochrane *et al.*, 1956), byssinosis (Schilling *et al.*, 1955), mental illness (Carstairs and Brown, 1958), peptic ulcer (Doll *et al.*, 1951), and many other conditions, have obtained for the first time true pictures of prevalence which can be linked with occupation and other social characteristics of vulnerable groups.

The study of cohorts developed recently by Case (1956a, 1956b) and others is another way of looking at vulnerable groups. Just as the field survey gives an accurate cross-section in time of community illness, so the cohort study gives a longitudinal section of the illness and mortality experienced throughout the life span of succeeding groups entering the study. The social and other influences playing upon individuals born at different times must differ markedly in their effects. The cohort study is particularly useful in the investigation of these effects and of diseases which are long in development. Mortality from many cancers has been looked at in this way and it is probable that such diverse problems as mental illness, delinquent behaviour and chronic bronchitis will yield something to this approach.

The prospective study.—A major difficulty in the study of disease has always been to go beyond the demonstration of associations and show that associated factors help to cause the disease. To show that associations are real and not spurious is a step in this direction. The reality of associations can be supported more easily if it can be shown that the data were collected prior to the onset of the disease. For example, when Doll and Bradford Hill (1952) sought to demonstrate the association between smoking and lung cancer, they were not satisfied of the reality of recollected (i.e. retrospectively associated) smoking habits of the 1,357 lung cancer patients. To confirm the reality of the association in their prospective study Doll and Hill (1956) demanded that the smoking habits of a group of healthy men be recorded and that these be linked with disease only when it occurred later on in the lives being studied. The prospective study is now being widely used in epidemiological inquiry. It will be most useful in probing associations such as, for example, those found between psychological disturbance and disease.

I now propose to discuss some examples of recent significant increases in medical knowledge which have led or will lead towards specific preventive

measures. They are selected to illustrate the various problems in prevention and they are taken largely from the non-infectious and chronic disorders and from obstetrics.

PREVENTION BEFORE 'CAUSES' ARE FULLY UNDERSTOOD—OBSTETRICS

Very small changes in obstetric practice have striking effects upon perinatal death rates and maternal mortality. Often lives can be saved by intervention even when the disease process is not clearly understood; for example in the toxæmias of pregnancy. To measure the size of the maternal mortality problem and to describe the factors concerned, the Ministry of Health has recently examined confidential reports upon the deaths of some 1,400 mothers, over 1000 of which were due to pregnancy (Walker *et al.*, 1957). It was estimated that about 400 of these deaths could have been prevented in the present state of knowledge. As a result these workers recommended hospital confinement for all multiple pregnancies, all mothers after the third child, all in whom any abnormality has been found as well as for all mothers over 35 years of age and primiparæ over 30 years of age. One interesting feature of this study was the suggestion that in about half of the 'avoidable' deaths the patient herself was in error in not seeking care early enough or in failing to carry out medical advice. It is possible that even for this type of error there is some medical responsibility.

Analyses of perinatal deaths of children (e.g. Baird, 1952) suggest that a large number of social as well as organic factors are involved. Without waiting to understand fully the interaction of factors or even the pathology concerned it is possible to use associations as diverse as social class, height or even occupation of father as well as age, parity, and the like, as indicators for early intervention. There is probably no other field where epidemiological findings can so quickly be turned to account.

PREVENTION BEFORE 'EFFECTS' ARE FULLY UNDERSTOOD—RADIATION

With few exceptions the biological effects of radiation are feared more than they are understood. Particularly, the full extent of the mutagenic and carcinogenic effects on man is not known. They are serious enough, however, to make the control of radiation a task of special importance (Medical Research Council, 1956). Apart from the most elaborate and efficient schemes of industrial safety yet seen in this country and an enormous volume of research, there have been one or two other small but significant advances. First, the setting up of biologically tolerable radiation limits (Medical Research Council, 1956), warnings about potentially dangerous sources of radiation (such as pedoscopes) and wide recognition of the dangers of repeated x-rays. Secondly, the pooling of expert knowledge in the form of an advisory bureau which offers a service to industry and medicine (the Medical Research Council Radiological Protection Service). In addition there have been several reports of devices designed to

screen particularly the young child from x-rays (e.g. Batten and Brown, 1956). Finally, the Medical Research Council has set up two new genetics units: one to study populations, the other to study clinical problems.

CANCER PREVENTION

Identification and control of the industrial cancer-producing agents is one of the most rewarding areas of preventive medicine. The studies of Doll (1955) on lung cancer in asbestos workers and of Case *et al.* (1954) on bladder tumours are interesting examples which illustrate recent discoveries. In the first, Doll set out to test the hypothesis that lung cancer was an occupational risk of asbestos workers.

> The mortality experienced by a group of men who had been working for at least twenty years in potentially dusty operations was examined with the most painstaking care. It was then compared with that expected from the group on the basis of the experience of all males of the same ages in England and Wales. Excess mortality that could only be due to chance once in one million times was encountered with lung cancer. Four possible explanations of this high mortality were then examined and it was decided that in the group studied the disease must be truly occupational.

Of great interest was the demonstration that preventive measures taken as far back as 1933 were helping to eliminate the disease—another example of prevention without exact knowledge of the cause.

In the second example Case and his colleagues were able to take a group of suspected carcinogens—the aromatic amines—and demonstrate the extent of the risk of bladder cancer run by workers using them. The firm demonstration by most convincing and exact epidemiological methods that these workers ran a risk some 30 times that of others has been a vigorous stimulus to specific preventive measures.

That *lung cancer* is to a large extent a preventable disease is now undisputed even by the tobacco manufacturers. Demonstrations of the association with cigarette smoking have surpassed in accuracy the majority of the day-to-day relationships in medicine which we are accustomed to look upon as 'causal' (Medical Research Council, 1957). The findings in this country of Doll and Bradford Hill (1950) have been supported by some two dozen other studies from seven countries, two or three of them 'prospective'. Edwards (1957) concludes that smoking is related to at least 84 per cent. of all cases of lung cancer in men and at least one-third of the cases in women.

Now that, for all practical purposes, a causal relationship may be assumed, the problem of smoking as an addiction must be faced and the problem of preventing it in the young adult be tackled. The long (20 years or so) 'incubation period' also focuses attention upon the teen-age and young adult smoker. We know very little about the pressures—social or personal—which govern smoking behaviour at these ages, but a start has been made by questioning schoolchildren as to their smoking habits (Jones, 1957; Raven, 1957). An interesting finding was that regular smoking in the young is more common among the less intelligent.

In a more recent unpublished study of 3,518 schoolchildren in London (Schilling and Chave, personal communication) one-quarter of grammar schoolboys and one-third of secondary modern schoolboys were smoking at least five cigarettes a week regularly by the age of 15 years (table I). About 1 in 8 of these boys were smoking 40 a week or more.

The increase in deaths from *leukæmia* (some 2½ times between 1931 and 1953) has been shown by many workers to be greater than could be expected

Age in years	Percentage of children of each sex in each type of school at each age who were 'regular' smokers (i.e. who smoked 5 or more cigarettes a week)				Total children
	Boys		Girls		
	Grammar	Sec. Modern	Grammar	Sec. Modern	
13	0.6	19.2	1.8	2.8	836
14	15.8	26.8	5.2	4.4	790
15	25.5	33.0	4.6	5.0	364
Total children	421	594	334	641	1,990

TABLE I.—Regular smoking among 1,990 London schoolchildren in 1958. (Unpublished material of Schilling, R. S. F., and Chave, S. P.)

from the improvement in diagnostic methods. Environmental causes for the odd geographic and social patterns of mortality as well as for the increase have recently been investigated. By far the most important cause appears to be ionizing radiations. Hewitt (1955) has drawn attention to the possible role of x-rays in the leukæmia of young children, and Stewart *et al.* (1958) have surveyed all malignancies in childhood between 1953 and 1955 in this country. They found that pre-natal x-rays of the fœtus, virus infections and threatened abortion of the mother were more common among the dead children than among controls. X-rays in infancy were also related to leukæmia in childhood. Whilst the recent increase in childhood leukæmia is not entirely explained by this study there is much evidence here that some leukæmia can be prevented by increased care and small dosage in x-ray examination and treatment. Another direct contribution is the finding by Court Brown and Doll (1957) that there was an excess of leukæmic deaths among patients irradiated for ankylosing spondylitis. In this case the research provided the best dose-response curves yet available, and gave some support to the contention that no radiation threshold exists in the genesis of this disease.

TOWARDS THE PREVENTION OF CHEST DISEASE

In the problem of chronic bronchitis, now causing some 5 per cent. of all deaths and at least 25 million days of sickness a year, three main preventable factors have been incriminated (Reid and Fairbairn, 1958). Apart from the

well-known association with poverty and low social class (General Register Office, 1958) there is reason to suppose that much of the mortality experienced by large towns is due to atmospheric pollution. Smoking undoubtedly plays a part and Edwards (1957), in reviewing the literature, feels that without it most cases would not occur. That the proportion of bronchitics in a group of men depends to a large extent upon smoking habits has been demonstrated by many workers (e.g. Palmer, 1954).

Brown, McKeown and Whitfield (1957) have shown that the association between bronchitis and social class in men in their seventh decade is only to be found among cigarette smokers, the non-smokers showing no such gradient. Oswald and Medvei (1955) have suggested that sex differences in the experience of bronchitis in one occupational group are due at least in part to differences in their smoking behaviour. Doll and Hill (1956) have shown what amounts to a dose response effect between smoking and mortality from chronic bronchitis among doctors, and many writers have ascribed the well-known association of chronic bronchitis, coronary heart disease, peptic ulcer and lung cancer to the common factor of smoking. Finally, in the postmen studied by Reid and Fairbairn (1956) there was a marked excess of illness early in the lives of the bronchitics, including asthma and other chest disease. These findings suggest that early definition of the vulnerable group is now possible although perhaps specific preventive measures beyond a rural and non-smoking life are not yet available.

ACCIDENT PREVENTION

Martin (1957) has shown the surprising fact that death rates from accidents are declining in all age-groups and for both sexes except the young adult male and the elderly. Whilst control of machines and of the environment must remain the most important way to prevent accidents there are individual and social factors also involved. Motor-vehicle accidents are an important example and one likely to increase enormously in seriousness (Glanville, 1954). The individuals concerned in an accident have not been studied as much as the surroundings, but in motor-vehicle accidents at least there is now reason to suppose that vulnerable children can be defined in terms of maternal care, family illness, housing and the like, as well as in the more usual ways of age and sex (Backett, unpublished material).

Drivers of motor vehicles have been studied only to a small extent in this country and then for the most part by insurance companies (e.g. Dunthorne, 1958). Alcohol has for a long time been known to impair driving ability and a useful study by Cohen *et al.* (1958) has indicated in what way driving changes. Not only did the experienced bus drivers taking part in this study become involved in more hazards after they had taken alcohol but judgment as well as performance deteriorated. Alcohol also intensified any tendency to overrate ability in relation to performance. The prevention of accidents due to alcohol is made more difficult by a popular attitude of tolerance. This attitude is fostered by official statistics. For example,

there is an important difference between independent estimates of the proportion of motor-vehicle accidents in which alcohol plays a part (perhaps as much as 50 per cent. of the 216,000 accidents in Britain in 1956) and the published estimate of the Ministry of Transport and Civil Aviation (994, or less than 0.5 per cent.). A long-awaited Medical Research Council report may focus attention upon this subject.

MENTAL ILLNESS

Carstairs (1958), in attempting a description of preventive psychiatry today, is guardedly optimistic but considers that progress will be slow until there is much more information as to etiology. In the meantime prevention based largely upon faith is being actively and sincerely pursued in many hospitals, child guidance clinics, schools and in the homes of young children by medico-social workers and health visitors as well as psychiatrists. It is not known whether the careful help which is given about, for example, breast feeding, separation, or about 'authoritarian' parents and teachers and many other aspects of mental hygiene does actually foster mental health or prevent mental illness. Until the results of controlled prospective studies are available preventive psychiatry must obviously continue along present lines.

The suggestion that some mental illness (particularly schizophrenia) is influenced by environment comes from a sharp social-class gradient in first admissions to hospital (Registrar General, 1958). If it could be shown that this apparent increase in incidence from Class I to V was real it would constitute a first step towards prevention. It may be due, however, to a combination of factors such as the drift of an upper-class patient through job after job to a lower social class before admission to hospital, or even to greater tolerance of mental illness in the richer, uncrowded household. On the other hand, there is evidence of the relation between mental illness and social conditions (e.g. Hare, 1956) which implies that some prevention is possible. It also seems likely that the chances of further breakdown among discharged hospital patients is related to the type of social group to which the patient belongs (Carstairs, personal communication). These studies open the way to eventual preventive action through a manipulation of the social environment—a way already being tried by Maxwell Jones (1952) and others.

SUMMARY

In the first part of this review attention has been drawn particularly to changes in medical attitude to prevention, to preventive aspects of social policy and to the newer epidemiological techniques used in preventive medicine. The second part mentions examples from recent research which have led or will lead to specific preventive measures. Examples taken are from maternal and perinatal mortality, industrial cancer, lung cancer and leukæmia, from chronic bronchitis, accidents and mental illness.

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ADVANCES IN DENTISTRY

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Dental caries must obviously take priority in any review of advances in dentistry. So far as prevention of this scourge of childhood is concerned, attention is still focused on fluoridation of water supplies and the influence of carbohydrates in the diet.

FLUORIDATION

Experimental fluoridation of water supplies is now being carried out in four selected areas in this country, and a further three-year study is involved before the full findings will be available. The case for fluoridation was reviewed by Wilkinson (1955) and the further evidence that has accrued since that time lends strong support to his observations.

More than 30 million persons in 1,426 communities in the United States are now drinking fluoridated water. Hill (1957) records the experience of three communities in Canada and the United States who have reported after a ten-year period. The three areas reported a notable reduction in the dental caries experience and even the 16-year-olds showed a reduction of 26 per cent. in dental caries experience in the permanent teeth. Recent studies on the medical aspects of fluoridation, about which concern has been expressed, suggest that the body does not lack metabolic experience of handling fluorine, and studies with radioisotopic F^{18} by various workers have reported on the high efficiency of the mechanism for the control of the concentration of fluoride in the blood and body fluids. For generations communities in various parts of the world have been using drinking water which contains fluorine in the recommended quantity and even five times as much but, as Hurny (1953) has shown in Sweden, apart from mottled enamel, no cases of fluorosis have been found among these people. A ten-year study of the medical aspects of excessive fluoride (8 p.p.m.) in the water supply in certain United States communities has also shown no detectable adverse results.

DIET AND CARIES

Davies (1954), reporting the results of two independent surveys on children in New Zealand, says that at two years, 45 per cent. have dental decay, and at six years 92 per cent. are affected. He asserts that the only methods for prevention of dental decay that have produced clinically successful results are restriction of intake of fermentable carbohydrates, notably the elimination of between-meals 'snacks', good oral hygiene and topical application of sodium fluoride. That they need to be initiated in the pre-school child is clear. He comments in passing on two extrinsic stains

affecting the deciduous teeth that often worry parents: (i) the green stain that is commonly found in the mouths of children of high susceptibility to dental decay, (ii) the black stain which is usually associated with low susceptibility to caries and has no pathological significance.

It is a disturbing experience to find how little understanding there is of the merits of rational dietary habits among, for example, boarding-school medical officers. The pernicious habit of tucking children up in bed with biscuits and milk, even although there is a perfunctory cleaning of the teeth afterwards, is a habit that should long ago have been abandoned. There are, of course, those who would prohibit sweets and who would like to close all our sweet shops. Such unworldliness merits a benevolent smile, particularly since there is evidence that the real enemy is the sticky carbohydrate with the long retention rate on the tooth surface or in the tooth crevice, and this may well be the sticky bun rather than the boiled sweet. The sucking of a boiled sweet after the consumption of sticky carbohydrate, bread for instance, is the perfect tooth-dissolving combination since the food plaques on the teeth are supplied with a steady supply of a simple sugar for conversion by the bacteria in the plaques to acid, and numerous investigators have shown the dangerously low pH that results and which persists for as long as three hours.

'Iced lollies' have recently attracted the attention of the public press in consequence of a study of fruit drinks and tooth erosion by Holloway, Mellanby and Stewart (1958). Children suck these frozen synthetic fruit cordials for long periods and expose the teeth to dangerously low pH levels. The investigation showed the marked erosive effects that follow and points the moral in the way of the reduction in erosive power that results from the addition of certain inhibitory substances. It is clear that we need to explore further the use of non-toxic inhibitory substances which will either promote the buffering action of the saliva or inhibit further acid production when the sugars present in the drink are retained by the bacterial plaques occurring on the children's teeth. It is perhaps too much to hope that they will abandon their lollies.

It is obvious that sticky carbohydrates should not be allowed later than two hours before bedtime if the danger of their retention throughout the hours of sleep is to be avoided and good sense dictates that the last meal should be terminated with portions of apple, carrot, turnip or even cabbage stalk which many children will be found to enjoy. Well chewed, these fibrous foods are more efficient than the man-made toothbrush. Rational dietary habits should include a shift more to the protein side from the present heavy carbohydrate bias.

Lødrup (1953), in a comparative study of the dental condition of the children of Bonn and Oslo, noted that, although the sugar intake in Bonn was markedly higher than that in Oslo, the caries incidence was notably lower. He came to the conclusion that because of their stagnatory qualities, bread and potatoes are more dangerous than sugar.

MALOCCLUSION

One of the major developments within the dental service during recent years has been the marked growth in demand for orthodontic treatment. The 1940 Guggenheim survey showed that 50 per cent. of children between two years and nine-and-a-half years had minor malocclusion whereas only 10 per cent. had severe malocclusion. The need for preventive orthodontics is very real to prevent the minor conditions developing. The interception and correction of bad oral habits are of the utmost importance: e.g. thumb sucking, atypical swallowing and tongue-thrusting habits. The serious dental deformities produced by excessive growth of adenoid tissues resulting in obstruction of the nasopharyngeal space are emphasized, and the greatly increased hazard of relapse after orthodontic treatment should be borne in mind if nasopharyngeal obstruction remains. Sclare (1957) has drawn attention to the marked influence of lower-lip posture on the position of the teeth and in many cases this is the one unfavourable factor of environment leading to unsightly protrusion of the upper incisors. Often only a mouth screen is needed to alter the lower-lip posture and to modify the tone of the lip musculature. The profound effect on the appearance and confidence of adolescents for whom this service is rendered is worthy of emphasis.

THE FRACTURED INCISOR

The tragedy of the fractured incisor in children from trauma is one that merits our concern and a conservative approach, particularly with regard to pulp preservation. Successful vital pulpotomy in the treatment of fractured incisors is a possibility which is too often neglected now that the effectiveness of calcium hydroxide as a pulp dressing is well established. Slack (1953) has demonstrated histologically the development of a new bridge of dentine at the site of the amputation. The saving of such teeth and the avoidance of collapse of the front teeth or of the need of a one-tooth denture has a profound psychological effect on a sensitive child.

CONGENITAL MALFORMATIONS

The concept of developmental arrest, although adequate in explaining cleft lip and cleft palate, is too limited a view and numerous contributions in the field of experimental teratogenesis are recorded. The embryology of cortisone-induced cleft palate has been studied in two strains of mice (Walker and Fraser, 1957). The work of McNeil (1954) on the non-surgical repair of hard-palate defects has excited considerable interest. By applying mechanical irritation of the marginal tissues he has stimulated ingrowth of bone and ultimate closure of the cleft.

DENTAL TRANSPLANTS

A fascinating hope for those who inadvertently lose a tooth in an otherwise intact dental arch is contained in a report by Apfel (1956) who reported the transplantation of a lower right third molar bud in a girl of 17 to the lower left first molar position. Under general anæsthesia, the bud was placed

well down in the alveolar bone, the wound closed with sutures and an acrylic splint placed over the transplanted tooth to hold the adjacent teeth in functional position. A year later the now erupted tooth was subjected to slight corrective positioning. X-rays show the excellent result seven years after transplantation.

PERIODONTAL DISEASE

Although dental caries continues to attract a major portion of the attention of the dental profession, there is a welcome increase in the attention given to the subject of periodontal disease. The relative importance of local and systemic factors has long been a controversial subject, and interesting work has proceeded on the subject of protein deficiency as a predisposing factor in periodontal disease. Lysine-poor diet was found to lead to disorganization of the attachment fibres of the periodontal membrane after a seven-week period and periodontal tissues exposed to mechanical irritants showed much greater susceptibility in the protein deprived groups. A study of the gingival condition of a group of children in England by Parfitt (1957) showed that the prevalence and severity of gingivitis reached a peak for boys at 13 years and for girls at 11 years and a seasonal incidence with slightly lower values in the August-November period.

CAVITY PREPARATION

The fear-producing propensities of the dentist's drill have contributed much to the general attitude towards dental treatment. It is of interest therefore to record the preoccupation with the technique of cutting enamel and dentine. The steel bur has been largely superseded by tungsten carbide drills and by diamond instruments. The resulting increased efficiency is a powerful factor in removing the patient's apprehension. A further factor in promoting more efficient cutting has been the increased speeds that are being employed. Speeds up to 100,000 r.p.m. are now being used, compared with the old one of 2000 r.p.m. High-speed cutting finds favour because quicker cavity preparation reduces the time involved for the patient and his discomfort, and more work can be done at one appointment, so reducing the number of visits. High speeds also involve a lighter touch with minimal pressure and vibration. Both air and water turbine-driven handpieces for holding the drill are being used. This vigorous approach to the vibration and pain factors holds hope that the patient of the future may yet find relaxation in the merry hum of the dentist's drill.

Ultrasonics—high-speed sound waves—have also been employed experimentally to replace the conventional rotating drill and a clinical study on 52 patients indicated that the treatment was without complications, and virtually painless cavity preparation is reported.

LOCAL ANÆSTHETICS

Parallel with the advances in tooth cutting goes the marked improvement in local anæsthetics. The clinical efficiency of lignocaine as compared with procaine has been fully established. In rapidity of onset, depth, extent and

duration of anæsthesia lignocaine is superior. Results also suggest that the lignocaine equivalent is well under one-half of the procaine dosage for comparable anæsthesia. The smaller doses further reduce the danger of the few toxic effects noted in a large series of injections.

DENTURE SORE MOUTH

The 'rubber sore' mouth was a well-known condition in the days of vulcanite dentures; now, in the plastics era, the acrylic sore mouth, or alleged acrylic allergy, is a not uncommon condition. Suffice it to say that true allergy is extremely rare and that the commonest causes of the condition are ill-fitting, shuffling dentures that are filthy and rough on the tissue aspect. The habit of wearing the dentures for twenty-four hours a day with only a perfunctory rinse in water places a strain on the oral tissues that is excessive. The habit of bruxism is widespread and increases the mechanical irritation of the tissues. Frequent sterilization of dentures in a weak hypochlorite solution, with attention to the fitting surface of the denture, will eliminate this condition in the great majority of cases. Further help is given by removal of the dentures at night. It is noticeable that there is a frequent association of the denture sore mouth with an angular cheilitis arising fundamentally from the collapse and infolding of the angular tissues, due to faulty dentures. In these cases the dental aspect is usually more important than the nutritional, and vitamin B complex often has little effect.

TEMPORO-MANDIBULAR JOINT PAIN

A condition that has excited increasing attention within the last four years is that of temporo-mandibular arthrosis. Hankey (1954) reports on the signs, symptoms and treatment of 150 cases seen in five years. He notes that women were affected three times as often as men and that 37 per cent. were between the ages of 20 and 30. Unilateral clicking was the most frequent complaint with a wide variety of other complaints, but nearly all symptoms were confined to the immediate region of the joint. The cumulative effect of altered stresses and strains on the joint imposed by malocclusion, loss of vertical dimension and loss of molar support was the most important etiological factor. Bite corrective treatment by splints and tooth grinding constituted the commonest form of treatment, supported by physical therapy. The view that the condition is a medical and dental problem and that solution is only possible by joint consultation has much to commend it, particularly in those cases which manifest an accompanying bruxism—a common situation. The psychosomatic aspect merits serious consideration and may avoid much unnecessary and mutilating treatment.

Inevitably cortisone derivatives have found their way into dental practice and find use topically as in aphthous ulceration in the mouth and by injection into the temporo-mandibular joint. Strean and Horton (1953) report relief of pain and improved mouth opening in five patients exhibiting limited movement of the mandible. A single injection of 0.4 ml. of hydrocortisone acetate saline suspension gave beneficial effects lasting up to

four months. In reviewing a series of 500 patients, Schwartz (1957) comments on early experiences in the temporo-mandibular joint clinic at Columbia University. Attempts to identify the many factors involved revealed the lack of stability of mandibular posture and movements in

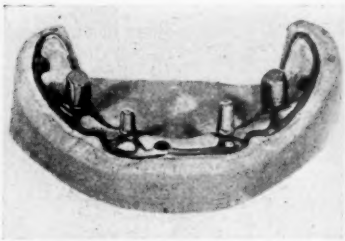

FIG. 1.—View of metal casting on plaster model of mandible, prior to subperiosteal positioning.

FIG. 2.—Intra-oral view of metal mandibular implant. Posts will carry lower dentures.

such patients and the prevalence of emotional tension. Stethoscopy was useful in the clinical examination of the joint movements. Bruxism was common and, although in some cases correct mechanical therapy resolved the condition, in others the condition evaded resolution. He comments wisely on the recent radical procedure of condylectomy that is being favoured, and the caution with which it should be considered.

Henny (1957) recommends high mandibular condylectomy for the resistant cases and describes the technique used on 20 patients who had not responded to conservative therapy. They had been treated for up to sixty months with various measures, such as rest, soft diet, occlusal equilibration, full mouth reconstruction, muscle relaxants and inter-articular injections of cortisone. In all cases high condylectomy with preservation of the meniscus, condylar neck and ligamentous attachments resulted in complete and lasting relief from pain. Postoperative function was said to be good and, although slight deviation of the mandible in the extreme open position was observed in half the patients, it was of no importance. Meniscectomy has been abandoned in favour of condylectomy, after comprehensive conservative therapy has failed to eliminate joint pain.

IMPLANT DENTURES

To those who are edentulous and whose alveolar bone has markedly atrophied life can be trying, with the intermittent discomforts of a shuffling lower denture coupled with poor masticatory efficiency. Interest therefore centres in any efforts that can successfully be made either to recreate the alveolus or to replace it. Blackstone and Parker (1956) report experimental and clinical experience with grafting procedures to the alveolar ridge in dogs and in humans. Complete osteogenesis was observed in about 130 days in the 50 per cent. successful results recorded.

Perhaps the most significant and yet controversial development lies in

the mandibular subperiosteal implant. Constructed in metal, a cobalt-chromium alloy, the appliance is laid on to the prepared surface of the bony mandible with projections passing through the replaced muco-periosteum and constituting posts, usually four in number, on which the lower denture is later constructed. Exacting technically, and full of hazards for the beginner, there is nevertheless a sufficient fund of knowledge to merit serious consideration for the claims made for this technique. Successful treatment enables the stress of mastication to be borne directly on the mandibular bone and no pressure is felt on the mucosa and the stability of the denture excites the enthusiastic reaction of the patient.

A report by Goldberg and Gershkoff (1954) reviews the progress attained during the previous six years in a series of 72 cases. They state that, whereas the full denture implant is not intended to replace conventional dentures, it is designed to give an added denture service for the difficult prosthetic patient. They recorded that upper jaw implants should be used only in extreme cases. Undoubtedly, the criticism of this technique centres around the nature of the union, if any, between the post and the soft tissues. The inert nature of the metal alloy used shows no tissue response and has led to Berman (1955) advocating the use of a polyvinyl sponge covering to the metal post whereby tissue infiltration into this material will seal off any entry between tissues and metal implant. Berman reports clinical and laboratory studies on this aspect of the problem. Trainin (1957) is the principal worker in this field in this country and figure 1 shows a completed case by him before placement of the denture. In his article he has reviewed the problem and gives case-histories extending over a period of eight years. Whilst the mandibular implant is the main consideration, there are variants of technique in other situations in the mouth, which he describes.

I am indebted to Mr. F. Boris Trainin for the loan of the photographs illustrating a typical mandibular implant.

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CURRENT THERAPEUTICS

CXXX.—TRANQUILLIZERS

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In the two years since we reviewed these drugs (Leiberman and Vaughan, 1956) their use has become widespread in medicine and psychiatry, and even something of a public health problem, as may be seen in the World Health Organization Special Report (WHO, 1957) where they are regarded as either habit forming or potentially habit forming.

In some parts of the world these drugs are readily available to the public. A recent issue of *Time*, for instance, reported that meprobamate is being freely sold in Japan under various names, and advertised with all the fear-inducing characteristics and low ethical standards associated with the patent-medicine trade in certain parts of the world. In Great Britain drugs of this class are not so freely available. They require a prescription or, in the case of those which do not, the retail pharmacists have agreed not to advertise them with displays which would tend to push their sales. Tranquillizers are big business. Any remedy which is really effective in the treatment of the neuroses or psychoses is assured of an immense sale, since from 20 to 40 per cent. of the illness seen by practitioners is neurotic, and mental beds form about half of the total hospital beds in the country. It is not surprising therefore that the resources of many drug manufacturers have been thrown into a search for new and more effective agents. Every few weeks sees another new compound presented with a fanfare of publicity, and claims which usually far outrun the known clinical data. It is only fair to add, however, that a large amount of genuine research has been undertaken, with the result that a number of new avenues to understanding the somatic basis of neurotic and psychotic illness have been opened.

Some eminent psychiatrists (Lewis, 1958) still express doubts as to their value, but there are now many reports of their effectiveness in the treatment of the psychoses, particularly the more chronic kinds. For example, an analysis of the population of the New York State Mental Hospitals for the year 1955-56, the first year that large-scale pharmacological therapy with tranquillizers (chlorpromazine and reserpine but mainly chlorpromazine) was used, shows that the residual population fell by 500 patients, reversing the trend of the previous decade which had shown an annual

increase of 2000 (Brill and Patton, 1957). This is impressive. These drugs are also being used on a large scale in British mental hospitals, and it would be reasonable to attribute some of the improvement and recent decrease in the chronic mental hospital population in this country to the use of these

Tranquillizers most effective in the psychoses and organic reaction states	
(1) Phenothiazine derivatives:	Chlorpromazine ('largactil') and other compounds.
(2) Rauwolfia alkaloids:	Reserpine ('serpasil'; 'serpiloid')
	Deserpidine ('harmonyl')
	Rescinnamine ('moderil')
Tranquillizers most effective in the neuroses and minor functional disturbances	
(1) Antihistamine substances:	Diphenhydramine ('benadryl')
	Promethazine ('phenergan')
(2) Substituted propanediols:	Meprobamate ('equanil'; 'mepavlon'; 'miltown')
	Phenaglycodol ('ultran')
(3) Diphenylmethane derivatives:	Hydroxyzine ('atarax')

TABLE I.—Classification of tranquillizers.

drugs. This trend can be seen more clearly in some hospitals than others. In one mental hospital the large-scale use of tranquillizers and other neuropharmacological agents combined with an extensive programme of general care resulted in the practical elimination of seclusion and 'shock' therapy, a trebling of patients on parole, and a 90 per cent. reduction in destructiveness (Ferguson, 1957). This is also our own general experience with these drugs in the treatment of chronic psychotic patients (Leiberman and Vaughan, 1957).

CLASSIFICATION

The total number of tranquillizers available has increased considerably since our last review, but from the clinical point of view they are still most easily considered in two main groups: those more effective in the psychoses and major psychiatric syndromes, and those more useful in the neuroses or minor psychiatric syndromes (table I).

The undoubtedly effective tranquillizers are the phenothiazine group and the Rauwolfia alkaloids, and the indications for their use are acute and chronic psychotic states and delirium characterized by overactivity and psychomotor excitement. The pathological physiology of these conditions is as yet unknown, and one is driven to speculate on the way in which the known pharmacological actions of these two groups of drugs and their undoubted therapeutic effectiveness could fit together. Both groups have multiple actions, and in the present state of knowledge it is difficult to pick on the particular one responsible. Both groups produce a Parkinsonian syndrome in large doses, probably due to a blocking action on the reticular formation of the brain stem, and both have a complex action on the hypothalamus, stimulating some functions and suppressing others. Chlorpromazine will block the action of lysergic acid diethylamide, a drug which will produce hallucinosis and mood and thought disturbance in susceptible individuals.

Reserpine releases serotonin from the brain and appears to block its action. Serotonin also antagonizes lysergic acid diethylamide. The relation of serotonin to abnormal mental states is purely speculative and the mode of action of lysergic acid is unknown. It may well be that the action of the tranquillizers will have to be sought in relation to the action of other neurohumeral agents, some known, such as noradrenaline, others as yet unknown.

At present the method of searching for new tranquillizing compounds is to test new drugs on a large number of widely differing functions of the nervous system of animals—electrophysiological, biochemical, behavioural and psychological—and compare the actions with those of the known tranquillizers. So far no more effective drugs than reserpine, rescinnamine and chlorpromazine have been discovered. The result of this, however, has been the multiplication of drugs with very similar actions, differing as little as one sulphonamide from another when tested clinically. This is the present situation regarding the phenothiazine derivatives. A large number has been developed recently, having very much the same properties. The following are some of the newer or better known of these together with brief notes on their main characteristics:—

(1) Chlorpromazine ('largactil')	Indicated in states of acute psychotic tension, restlessness, and aggressiveness: i.e. acute and chronic psychoses; toxic confusional states and delirium tremens; senile and pre-senile dementia; mania; certain children's disorders. The toxic effects are: jaundice (2 per cent.), rashes (10 per cent.), blood dyscrasias (a few deaths); high dosage causes Parkinsonism—not always reversible. Dose: 25 to 800 mg. daily.
(2) Promazine ('sparine')	One-third as active as chlorpromazine. Same indications for use. May be useful for alcoholic confusion. Said not to damage the liver. ? more complications than chlorpromazine. Dose: 25 mg. upwards.
(3) Pecazine (mepazine; 'pacatal')	Less powerful than chlorpromazine, and not as effective in the psychoses. Claimed to have good effect on the agitation of senile depressed patients and senile psychoses, but we have not found it particularly effective. ? more toxic than chlorpromazine. Dose: 25 mg. upwards.
(4) Acepromazine (acetylpromazine; 'notensil')	Twice as powerful as chlorpromazine. Said not to damage the liver. ? more complications than chlorpromazine. Dose: 10 mg. upwards.
(5) Perphenazine ('trilafon')	Similar to chlorpromazine. Reports of Parkinsonism, torsion spasm, and muscle dystonia. Dose: 25 mg. upwards.
(6) Triflupromazine ('vespral')	Said to be non-toxic; rapid effect, without drowsiness. Dose: 25 mg. upwards.
(7) Thiopropazate ('dartalan')	Said to be less toxic than chlorpromazine. ? may cause liver damage. ? may be mildly epileptogenic. Dose: 10 mg. upwards.
(8) Methopromazine ('mopazine'; 4632 R.P.)	? less effective than chlorpromazine. Dose: 25 mg. upwards.
(9) Prochlorperazine ('stemetil'; 'compazine'; chlormeprazine)	As effective as chlorpromazine. ? better for psychoneuroses. ? no liver damage. Dose: 5 mg. upwards.

TRANQUILLIZERS IN THE PSYCHOSES AND MAJOR PSYCHIATRIC SYNDROMES

Chlorpromazine and reserpine continue to be used extensively in acute and chronic psychoses when there is psychomotor overactivity and excitement, but some withdrawn and stuporose patients will at times respond. Chlorpromazine is generally considered more effective than reserpine. It has been suggested that chlorpromazine is more effective in paranoid and schizo-affective disorders, and reserpine in the hebephrenic and catatonic states (Rudy *et al.*, 1956). Both are less useful in affective disorders. The main indications are acute and chronic psychoses, toxic confusional states and delirium tremens, senile and pre-senile dementia and confusion, mania (50 to 70 per cent. of cases will respond), and certain children's disorders. Individual responses are extremely variable and the dose has to be determined for each patient. The dose for chlorpromazine will range from 50 or 100 mg. daily by mouth to 600 or 800 mg. daily. When a rapid effect is required, as in toxic confusional states, repeated intramuscular doses of 75 to 100 mg. combined with general measures for restoring fluid and vitamin levels are usually adequate. For an immediate effect, up to 200 mg. may be given intravenously, well diluted in saline.

Hitherto, of the Rauwolfia compounds, reserpine has been used almost exclusively, but a recent report suggests that rescinnamine may be more potent clinically (Malamud *et al.*, 1957). The dose for rescinnamine is the same as for reserpine, 1 to 15 mg. daily.

Jaundice due to chlorpromazine has become a recognized hazard, and cases due to this are being admitted to general hospitals. The prognosis is good if the drug is withdrawn and appropriate treatment given. Chlorpromazine and reserpine have been implicated in asphyxial deaths due to impacted foodstuffs in chronic psychotic patients, said to be due to difficulties in swallowing while under medication with these drugs (Hollister, 1957). Asphyxial deaths in mental hospital patients, however, are not uncommon as a result of impaction of food in the larynx, and were well known before the days of tranquillizers, and inquiry of colleagues working in this field does not suggest that there has been any noticeable increase of deaths from this cause.

Prolonged sleep treatment or continuous narcosis can be induced and maintained using combinations of chlorpromazine, promethazine, and a barbiturate, and for added effect reserpine may be included. But whether the use of these drugs for narcosis has any advantages over the older combinations of barbiturates and paraldehyde is uncertain. Acute psychotic excitement and agitation can be more quickly controlled with convulsive therapy than tranquillizers, although the use of chlorpromazine concurrently may markedly diminish the amount of convulsive therapy required. Care must be taken, however, when using this combination as convulsive therapy following the recent administration of reserpine or chlorpromazine may cause collapse due to a sudden fall in blood pressure. It is safer to start the

tranquillizer in full doses as soon as the excitement and overactivity are responding to the convulsive therapy.

TRANQUILLIZERS IN THE NEUROSES

Meprobamate ('equanil'; 'mepavlon'; 'miltown') is still the most popular of the tranquillizers for the neuroses, although a number of new drugs have come on to the market. Clinical reports as to its efficacy vary widely. It is probably most used in states of tension, mild anxiety, and persistent insomnia. It is not a very efficient tranquillizer, and it may cause addiction, dermatitis, purpura, diarrhœa and convulsions (*J. Amer. med. Ass.*, 1957). A new compound, phenaglycodol ('ultran'), has been introduced recently. It is related chemically to meprobamate and the general indications for its use as well as its side-effects appear to be the same. Another new drug, hydroxyzine ('atarax'), has both a mild sedative action and a tranquillizing action. It is related to azacyclonal ('frenquel') and benactyzine ('cevanol'; 'lucidil'; 'nutinal'; 'suavitil') and may be useful in obsessional states and tics as well as general minor anxiety and tension, but it does not appear to have any very special advantages over the other mild tranquillizing agents. In states of mild anxiety, particularly when this occurs mainly at night, diphenhydramine ('benadryl') or promethazine ('phenergan') may be very effective and free from toxic side-effects.

A careful study by Raymond *et al.* (1957) suggests that chlorpromazine, benactyzine, and meprobamate are no more effective than amylobarbitone in relieving neurotic symptoms.

TRANQUILLIZERS IN GERIATRIC PSYCHIATRY

There have been many reports on the use of tranquillizers for geriatric disorders. The majority of these show that patients with simple deterioration, paranoid states, senile depressions and cerebral arteriosclerosis may all be helped, particularly when they are agitated, destructive, irritable and resistive to nursing care (Tennent, 1957). There is no doubt that active phenothiazine compounds and reserpine, alone or in combination, together with analeptic drugs of the amphetamine group, or leptazol, by mouth will produce improvement in many apparently deteriorated senile patients.

TRANQUILLIZERS IN CHILD PSYCHIATRY

Tranquillizers are not curative in children's disorders but, by providing a temporary period of freedom from gross disturbances, they are a valuable addition to other methods of treatment. They can assist in relieving the anxiety of the child and that of the parents for a short time, after which it may be possible for the child to resume his normal processes of development. Chlorpromazine and promethazine may be useful in this way for acutely disturbed, hyperactive, agitated and aggressive children (Bender and Nichtern, 1956; Annell, 1957), schizophrenic children, and certain overactive children with brain damage, although sometimes the latter may become

more disturbed. Chlorpromazine may be given in doses of 10 to 200 mg. daily according to the age and condition of the child, in tablet form or as the elixir. Diphenhydramine may be effective in primary behaviour disorders, impulsive behaviour, tics and repetitive motor disorders and there have also been encouraging reports of hydroxyzine in these conditions (Segal and Tansley, 1957). The analeptic drugs, amphetamine and dexamphetamine, have also a tranquillizing action in children with neurotic overactive behaviour patterns. Chlorpromazine and reserpine may effectively control noisy, aggressive and destructive defectives (Sprogis *et al.*, 1957; Horenstein, 1957; Tarjan *et al.*, 1957), although it appears that in children reserpine is more variable in its effects than in adults. Finally there have been some interesting reports on the use of meprobamate in minor motor seizures (Livingston and Pauli, 1957), stammering, enuresis, and cerebral palsy (Gillette, 1957).

DISCUSSION

The present position of the tranquillizers in psychiatry is that there are two groups of drugs, the phenothiazine compounds and the Rauwolfia alkaloids, which have a specific action on some of the symptoms of psychosis. Alone or in combination with other drugs they are effective in acute and chronic psychoses mainly characterized by psychomotor overactivity and excitement. States of depression or stupor either do not respond, or are better treated by other means, such as convulsive therapy or analeptics. The neuroses are no more responsive than to other agents.

The phenothiazine compounds are in general more effective than the Rauwolfia alkaloids, although individual patients show marked differences in their responses to one or other of the groups of drugs, and combinations of a phenothiazine compound with reserpine or with another phenothiazine compound, e.g. chlorpromazine and pecazine, may be more effective than either singly. Little can be said at present about specific indications for particular drugs. Their action, like the action of other forms of physical therapy in psychiatry, cuts across diagnostic categories. The most effective dose of both groups is reached at a level where they cause motor slowing and rigidity: a level when Parkinsonian symptoms are appearing. Parkinsonian symptoms can be controlled in some cases with anti-Parkinsonian drugs if it is necessary to maintain a high dosage level. Usually the dose can be reduced once symptoms are under control, and patients may be discharged from hospital and maintained on quite low doses. When patients are discharged from hospital after treatment with tranquillizers, the burden of their supervision usually falls on the general practitioner, although some hospitals are now starting special maintenance clinics for this purpose. It is clearly important that the practitioner should not only recognize the possibility of toxic symptoms, but should also be aware of the importance of maintenance therapy, which for some patients is as important for the control of psychiatric illness as it is in the case of digitalis for the cardiac patient.

In the treatment of neurosis none of the tranquillizing agents is more effective than the barbiturates, and some are more toxic. The barbiturates are far from ideal, they tend to cause addiction, and are a ready means to suicide, and an efficient tranquillizer would be most useful in this field. We still await an efficient drug to relieve anxiety and the symptoms that go along with it without toxicity or the danger of addiction. Some authors (Laurence and Pond, 1958) consider that an efficient drug in this respect might have undesirable social consequences, and that it would be better to strive to alter the environment than to search for the perfect tranquillizer for neurotics. Utopia, however, is far away, and the sufferers clamour for relief. Moreover, it is an oversimplification to suggest that neurosis anxiety is directly related to environmental stress: it is as often the result of disorganization of the patient's private world, and is one of the penalties we must pay for having a highly developed nervous system. Even Utopians will require an occasional dose to allay the anxiety inseparable from existence, although they may be materially in a better position to face it.

Tranquillizers are having remarkable effects in the treatment of the psychoses, particularly for chronic schizophrenics for whom it has not hitherto been possible to do a great deal in the control of their symptoms. Research is being stimulated into the physiology and biochemistry of mental disorders, and also into the best way of rehabilitating recovered and improved psychotic patients who have been ill a long time. In our opinion tranquillizers are another forward step in the physical approach to psychiatric treatment and promise a bright future for the growing science of neuropharmacology in the alleviation of mental illness.

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MINOR SURGICAL PROCEDURES

X.—OCULAR FOREIGN BODIES

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'And now I see with eye serene'—Wordsworth.

In our early biology lessons we learned that a minute extraneous fragment of matter in an oyster's shell can be the nucleus of a pearl of great price; and so a minute foreign body on the outside of the eye, or intra-ocularly, can cause great discomfort, quite disproportionate to its size, and complications up to and including loss of the eye.

CLASSIFICATION

Extra-ocular.—A foreign body may lie loose in the conjunctival sac, moving here and there, with the movement of the eye; it may lie embedded in the surface of the conjunctiva lining the lids or in the bulbar conjunctiva; it may lodge in the subtarsal fold, the shallow groove which runs along the inner surface of the upper eyelid immediately above the sharp margin of the lid and which can be seen only when the lid is everted; it may lie on the corneal epithelium; or it may be fixed in the epithelium or embedded in the cornea.

Intra-ocular.—A foreign body or missile which has penetrated the coats of the eye by perforating the cornea or sclera—and so comes to lie in the interior of the eye; in the aqueous chamber; embedded in the iris; buried in the lens; floating, as it were, in the vitreous; or thrust into the retina—is called an intra-ocular foreign body.

INCIDENCE

The most common accident met with in ophthalmology is that of a foreign body on the surface of the eye. In the eye hospital of a conurbation with over a million population the total number of new outpatients, including casualties, from January to June inclusive of the current year was 11,670: of these, 4,030 attended for the removal of extra-ocular foreign bodies, that is 34·53 per cent. In other words, of 90 new outpatients a day 30 were foreign-body cases. This is only a portion of the total number, for many are removed at home, by fellow-workmen, by factory and district nurses, by the local pharmacists and by the practising doctor to whom the victim turns when others have failed.

TYPES OF FOREIGN BODY

In domestic life there are hazards from ashes, coal dust and tobacco ash. Not infrequently, babies are the victims of cigarette ash inadvertently dropped by the mother into the suckling's eye. Eyelashes are rubbed loose and enter the conjunctival sac and scraps of ceiling-plaster and fragments of textile material are often found.

In industry, fragments of metal from tools, flakes of grindstone, dust from loose cargo, debris from building operations and iron and dust in boiler-making and ship-scaling are frequent sources of ocular foreign bodies in an industrial community.

As casual accidents, dust from cinder-paved 'blitz' sites gives much work to casualty departments, and street-dust at windy corners and sparks from engines add their quota. In the garden and country, thorns from hedge-trimming, husks of grain and chaff, insects or parts of insects find their way within the lids. In the tropics we often find the condition of myiasis in which flies enter the conjunctival sac and deposit their ova which hatch into larvæ. In West Africa I have seen a lively batch of fruit-fly larvæ wriggling in the upper fornix. The ocular foreign bodies associated with warfare are optimistically omitted from this review.

CLINICAL EFFECT

If the foreign body is smooth or soft it may cause no more than a mild irritation; but, if it is hard and gritty, at the moment of contact there is a sharp burning pain, a reflex flush of tears, and instant closure of the eyelid. The eyelid is usually rubbed; whilst this may succeed in ejecting the offending matter in a flow of tears it more usually causes an abrasion of the cornea or the impaction of the foreign body in the corneal epithelium.

The local irritation, supra-orbital headache, photophobia and lacrimation remain until the foreign body is removed or until it becomes embedded in the cornea so that its sharp corners no longer impinge upon the conjunctiva of the eyelid. These deeper foreign bodies, however, give rise to uveal irritation and circumcorneal injection. The wing of an insect or the diaphanous pellicle of a flower-petal or fragment of chaff may lie firmly adherent on the cornea and cause scarcely any discomfort and in appearance may resemble a corneal scar or nebula, but, if allowed to remain, ulceration will develop.

DIAGNOSIS

In many cases the patient gives a history of the incident but in other cases there is no history other than that one eye rapidly became sore and irritable and the history is that of an acute conjunctivitis. Acute conjunctivitis, however, is rarely unilateral and in every case of unilateral conjunctivitis a foreign body should be suspected and searched for. An ulcer may actually have developed without a foreign body being suspected. When the eye is

irritable and blepharospasm is present so that the lids cannot be kept open actively or even pulled apart, a drop of local anæsthetic, 1 per cent. cocaine or, better still, 1 per cent. amethocaine, should be instilled. Figure 1 shows the instruments and equipment required for the removal of an extra-ocular foreign body.

It is important that the examination should be made in a good light. The foreign body may immediately be seen in the cornea or on the bulbar

FIG. 1.—Tray laid out with sterile instruments and other equipment required for removal of an extra-ocular foreign body.

conjunctiva. A drop of fluorescein will often reveal an abrasion and a small foreign body. If it cannot be seen, then the lower eyelid should be pulled down exposing the lower fornix and the palpebral conjunctiva. If absent there, the upper lid must be everted.

Eversion of the upper lid.—This often presents unnecessary difficulty. The first direction to the patient must be 'look down'. A recollection of the anatomy of the lid will recall that the upper lid is stiffened by the tarsal plate. When the lid is raised the tarsal plate slides under the upper bony margin of the orbit, just as a garage door rises to lie under the ceiling. If the lid is in this position it cannot be everted. When the patient looks down the upper edge of the eyelid is grasped firmly between the finger and thumb and the lid can be turned inside-out as easily as the edge of a cuff can be everted. The foreign body will often be found lurking in the subtarsal groove. If it is not found there the upper fornix is inspected. The lid is still held everted, the patient continues to look down and a finger of the other hand pushes the lower lid inwards to rotate the eyeball. The loose fold of the upper fornix then pouts into view revealing a foreign body in its fold.

The foreign body may still elude observation because it is minute or translucent. If such a foreign body is embedded in the cornea its presence may be indicated by an irregularity in the *window reflex*. This is the mirrored picture of the window or light reflected by the corneal epithelium. An

FIG. 2.—A foreign body needle.

embedded foreign body causes an irregularity or break in the outline of the reflex. A more minute examination may require to be made with a corneal loupe—a x 10 lens held close to the observer's eye and approached to within one inch (25 mm.) of the patient's cornea. Such an adjunct is essential in searching for the tips of hedge-thorns or the minute spines from the pericarp of a horse-chestnut (*Aesculus hippocastanum*).

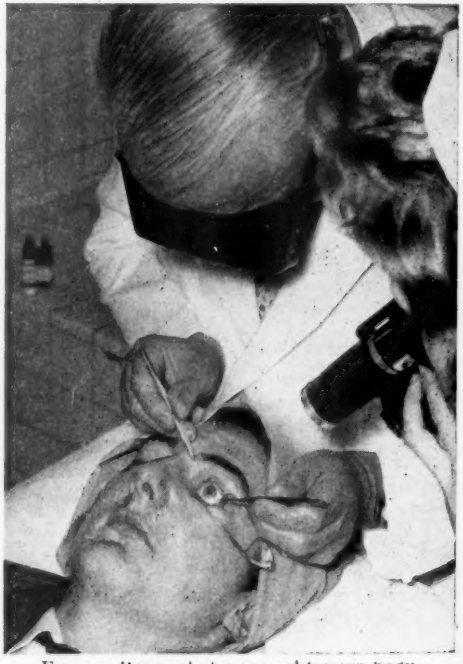

FIG. 3.—Removal of a corneal foreign body.

REMOVAL OF FOREIGN BODY

A pledget of cotton-wool should be rolled into a stiff 'pencil' and the foreign body wiped off. Even a foreign body which is partly embedded in the cornea will often respond to this method without recourse to cold steel. If it does not come off then the eye should be well anæsthetized with amethocaine, the patient having been placed on a couch or a chair with a head-rest so that the head is immobile. The lids are then retracted with a speculum or lid-hooks. A foreign-body needle (fig. 2)—a minute spearlike knife—is placed at the edge of the foreign body and the foreign body prized out (fig. 3). The old-fashioned spud with its rounded end should not be used: this makes a gutter or furrow in the epithelium and sometimes inflicts more damage than the foreign body itself. A drop of sulphacetamide or chloram-

pher ol is instilled and, if there is circumcorneal injection, betokening uveal irritation, a drop of 1 per cent. atropine sulphate. The eye is then covered with a pad and bandage or strapping and kept covered for twelve hours until the crater is epithelialized. It is advisable to request the patient to return for inspection twenty-four hours later. The patient does not always respond by doing so, but, in these days of 'litigation-happy' patients, should complications and litigation ensue, a point is scored against the doctor if he has not given this instruction or advice.

Cortisone should *not* be used in the first instance in the treatment of an abrasion or ulcer of the cornea.

COMPLICATIONS

Infection.—Intact corneal epithelium is proof against the attack of most organisms but when even the epithelium has been superficially abraded organisms readily enter and infection may ensue causing lesions of varying severity such as a superficial ulcer; a corneal abscess; a hypopyon ulcer, which is an irregular, sloughing ulcer accompanied by pus in the anterior chamber; and endophthalmitis in which the interior of the eye becomes, in effect, an abscess cavity. Secondary glaucoma almost invariably occurs and loss of the eye may be the end result.

Infection is due to one of three causes. It may (a) be introduced by the foreign body itself, (b) result from a non-sterile instrument and maladroit attempts to remove the foreign body, or (c) arise from infection in the conjunctival sac which in any case is rarely sterile. In this connexion it should be borne in mind that a mucocele, following lacrimal obstruction, is often a reservoir of pneumococcus and that this organism is a common cause of hypopyon ulceration. A man who is a boiler-maker, ship's painter and so on who is at hazard, and who has a mucocele, should be advised to have this condition dealt with not only because of its nuisance value in causing lacrimation but because of its potential danger.

Signs of infection.—The first stage of infection is a greyish ring in the corneal tissues surrounding the foreign body, or its crater if it has been removed. This is due to round-cell infiltration. At this stage there is uveal irritation with the circumcorneal redness of ciliary injection. The untreated ulcer becomes deeper, the edge of the crater breaks down irregularly and the base of the ulcer is lined with a yellowish slough. Iritis, with synechiæ, may develop and a line of yellowish pus is seen in the lower part of the angle of the anterior chamber obscuring part of the iris. The ulcer may perforate with destruction of part of the cornea, or endophthalmitis may follow.

Treatment.—Careful and aseptic removal of the foreign body followed by adequate treatment thereafter is the most effective prophylaxis. The advent of antibiotic drugs has greatly reduced the incidence of infection but if infection should supervene hospital treatment is essential. The ulcer may be carbolized or cauterized; antibiotics used locally and parenterally;

atropine instilled to control the iritis and an electric eye-warmer applied. Finally, surgical treatment may be indicated.

Lesser complications.—If Bowman's membrane has been injured then a permanent opacity will remain. If this is peripheral the visual function is not impaired but if it is central, visual acuity is reduced depending upon the density of the opacity. In cases of dense central opacities corneal grafting may restore the transparency of the cornea. The rust ring left by an iron foreign body may be removed either when the foreign body is removed or twenty-four hours later when the tissues have softened; but if removal is likely to cause trauma the rust ring is best left alone.

DISPOSAL OF FOREIGN BODY

The importance of retaining a foreign body, whether removed from the conjunctival sac, from the cornea or from the interior of the eye, cannot be sufficiently emphasized. The foreign body is placed in a double layer of 'sellotape' and the package taped on to the casualty-card or case-sheet. Thus retained, it may be a valuable piece of evidence to assist in determining for instance, whether it is a piece of metal from a tool or a foreign body which has blown in adventitiously.

INTRA-OCULAR FOREIGN BODIES

Although the treatment of an eye injury in which a foreign body has penetrated the coats of the eye is beyond the scope of minor, casualty-department surgery, a short description of the localization and removal may be of interest. The wound of entrance may be obvious, or the missile may have penetrated the eyelid and entered the eyeball behind the reflection of the conjunctiva. A careful search should be made with the ophthalmoscope. A foreign body which has recently penetrated the globe may leave a chain of glistening air-bubbles in its passage through the vitreous and may be seen lying on the retina. In other cases, intra-ocular hæmorrhage may prevent any possibility of its being seen. In these cases, x-ray investigation and localization is essential.

RADIOLOGICAL LOCALIZATION

Localization of foreign bodies in the eye must depend upon their radio-opacity. Foreign bodies which are non-opaque to radiation cannot be localized. Fortunately for the radiologist the foreign bodies which are most likely to penetrate the globe are made of hard material, most often metallic, and are therefore demonstrable.

The first step is to demonstrate that a foreign body is present. Careful technique is essential. In many departments special cassettes and screens are set aside for this purpose to avoid their contamination by marks and debris; in this way artefacts, confusing to interpretation, are avoided. Some radiologists prefer to use non-screen films to overcome this risk. The following views are taken:—

(1) A postero-anterior view in the nose-chin position, the tube being tilted 30° towards the feet so that the shadow of the petrous part of the temporal bones is cast below the orbits, giving a clear view of them.
(2) A lateral projection, as in a lateral view of the skull, except that the central ray passes through the outer canthus.
(3) Vogt's view is sometimes taken. This is a view of the anterior chamber taken laterally on a dental film. It is sometimes useful to show semi-opaque foreign bodies situated anteriorly.

Having demonstrated the presence of a foreign body it can now be localized by a choice of methods. The simplest method is to stitch to the

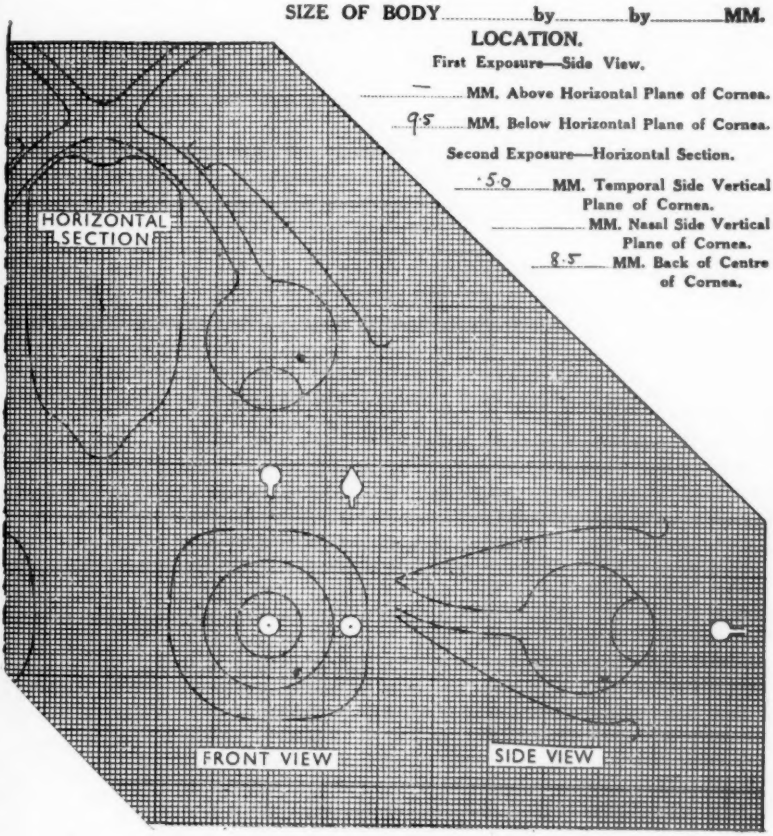
SIZE OF BODY ..... by ..... by ..... MM.
LOCATION.
First Exposure—Side View.
..... MM. Above Horizontal Plane of Cornea.
95 MM. Below Horizontal Plane of Cornea.
Second Exposure—Horizontal Section.
·5·0 MM. Temporal Side Vertical Plane of Cornea.
..... MM. Nasal Side Vertical Plane of Cornea.
8·5 MM. Back of Centre of Cornea.
HORIZONTAL SECTION
FRONT VIEW
SIDE VIEW

FIG. 4.—Localization chart—Sweet's method.

limbus a Stallard localizing ring. The foreign body can then be localized in relation to the ring. A method in common use is that devised by Sweet, but which has now been modified. The apparatus consists essentially of two

metal objects: a ball and a cone which can be spring-triggered to rest at a known position exactly in front of the cornea. Lateral films are taken so that the cone and ball are shown on the film, at first superimposed and then separated. The principle of the method is that if we know the position of two known objects, a third can then be localized in relation to them and the position of the foreign body can then be plotted on a special graph (fig. 4), which will show the relation of the foreign body to the horizontal and vertical planes and its depth from the cornea.

REMOVAL OF AN INTRA-OCULAR FOREIGN BODY

An intra-ocular foreign body is either magnetic or non-magnetic. If the former, removal is facilitated by the use of the giant-magnet. When the conical point of the electro-magnet is approximated to the eye the patient may be aware of movement within the eye; the iris may be seen to flicker if the foreign body is enmeshed in it; or the sclera may bulge towards the point of the magnet. The sclera is incised, pre-fixed sutures are inserted, the lips of the wound are drawn apart and the magnet applied to the opening. A magnetic foreign body will often spring to the point of the magnet and can then be withdrawn and the wound closed. If the foreign body is non-magnetic the sclera is opened at the nearest point to the localized foreign body, along the line of a diathermy burn which limits scleral and choroidal hæmorrhage. Fine forceps are inserted to grasp, if one is fortunate, and withdraw the foreign body. In all cases of removal or attempted removal of a foreign body systemic penicillin is injected as a prophylactic measure.

RETAINED FOREIGN BODIES

Retained foreign bodies may lie inert indefinitely and the eye may settle down with useful vision; but in many cases uveal irritation and inflammation persist with a risk of endophthalmitis or, worse still, sympathetic ophthalmitis. In such cases, particularly if the vision is greatly impaired, it is unwise to retain the eye. Air-gun slugs are particularly dangerous in this respect. They are non-magnetic, they are made of lead, which itself is toxic to the eye and, in that the muzzle-velocity is low, they are not heated and sterilized by passage through the air and so are often grossly infected. Legislation could help to reduce this slaughter of the eyes of the innocents, or not-so-innocents: just as compulsory use of eye-guards and protective goggles could reduce much trouble in industry. The accidental or adventitious foreign body will, however, always be with us and knowledge of how it should be dealt with will save many eyes and much distress.

My thanks are due to Dr. John Ross for his account of localization; to the Records Officer and the Photographic Department at St. Paul's Eye Hospital, Liverpool, for statistics and photographs, and to Messrs. John Weiss & Son Ltd. for the block for fig. 2.

REVISION CORNER

OPHTHALMIA NEONATORUM

A GENERATION ago ophthalmia neonatorum was still the major blinding affection of infancy; in the five years, 1950-54, not a single case of blindness was reported from this cause. This has come about not only because of better treatment but also because the incidence of the disease has gone down markedly. In 1920, over 10,000 cases were notified; little more than half that number were notified in 1930; the figures remained fairly stationary for the next ten to fifteen years or so, and in recent years the annual number notified has been around 1,700 and is still declining. It is likely that the type of affection has also changed. Whatever may have been the case in the past, it is clear that in recent years ophthalmia neonatorum has not been due mainly to the gonococcus. *Staphylococcus aureus* is today the commonest organism, responsible for about 35 per cent. of cases, with the gonococcus responsible for about 25 per cent. and many other organisms, including bacilli, accounting for some 20 to 25 per cent. In some 10 to 20 per cent. of cases no micro-organism can be found in the smear or culture. Most of these 'negative' cases do not represent faulty bacteriological examination, as was once thought, but are examples of ophthalmia neonatorum due to a *virus infection.* This virus has not been isolated in culture, but its existence has been demonstrated by animal inoculation, and by the presence of inclusion bodies in the conjunctival epithelium—a finding responsible for the designation of inclusion ophthalmia neonatorum, or inclusion blennorrhœa. The incubation period of inclusion blennorrhœa is generally 6 to 12 days (instead of 3 to 5 days in bacterial ophthalmia neonatorum). In other respects inclusion blennorrhœa is clinically identical with other types of ophthalmia neonatorum. Inclusion blennorrhœa is part of a clear-cut venereal disease. In the mother of the affected baby a scraping of the epithelial cells taken from the transitional lining at the os of the cervix generally also shows inclusion bodies. To complement ophthalmia neonatorum in the baby and inclusion cervicitis in the mother there is the non-specific urethritis in men in which inclusion bodies can also be demonstrated in epithelial scrapings. This virus infection seems to be fairly widespread in the community; it gives minimal clinical symptoms, and not infrequently it is subclinical.

PROPHYLAXIS

The *essential measure of prophylaxis* in ophthalmia neonatorum is the treatment of maternal infection during pregnancy. In the light of present knowledge this means more than the treatment of active or chronic gonorrhœa, or even of leucorrhœa. Ophthalmia neonatorum will be eliminated only when maternal infections are eliminated.

The more *immediate method of prophylaxis* associated with the name of Credé is immensely valuable, but has distinct limitations. The mechanical part of the procedure—cleansing of the lids as soon as the head is born and before the baby is allowed to open its eyes, and care being taken to prevent any contaminated bath water reaching the baby's eyes—is now part of the routine of delivery, and is consistent with the principles of asepsis. The chemical component of the procedure, the instillation of silver, or some other disinfectant into the eye, is of doubtful value and is a relic of Listerian antisepsis. It is a moot point if an infected conjunctival sac will be disinfected by the application of one drop of an antiseptic. There is little to support that assumption, and the recent tendency to discard prophylactic drops has not led to any disasters. The irrational basis of 'prophylactic drops' is emphasized by the fact that many of these drops are inactive or distinctly poor antiseptics.

TREATMENT

Sulphonamide therapy.—Employed locally the sulphonamides are useless in ophthalmia neonatorum, as they are inactivated by pus and break-down products of the tissues: given by mouth they are highly effective. When the baby is first seen a swab of the pus is taken both for a smear preparation and for a culture. The eyes are then irrigated with bland lotion, such as half-normal saline solution at room temperature; 1 per cent. atropine sulphate drops and drops of medicinal paraffin are instilled as a routine measure, and a tablet of sulphadimidine (0.5 g.) crushed into powder is given by mouth in a teaspoonful of water or milk. Sulphadimidine administration is continued in doses of 0.25 g. every four hours, day and night, until forty-eight hours after a clinical cure is obtained. Local treatment consists in three-hourly irrigation with a saline solution during the first day in cases with profuse discharge; as a rule there is no need for further irrigation on the subsequent days. After irrigation, medicinal paraffin is instilled as a precaution against the sticking together of the lids. Atropine is instilled three times daily in cases with corneal haze or ulceration.

With this treatment, swelling of the lids generally subsides within twelve hours after admission; purulent discharge disappears within twenty-four hours, so that a threatening purulent ophthalmia becomes a simple conjunctivitis giving no anxiety. The eyes are either dry or very nearly so within seventy-two hours.

The dreaded corneal complications of ophthalmia neonatorum do not develop. Some 40 per cent. of all babies show complete clinical cure within three days, and 90 per cent. are cured within eight days. Such cases as are resistant to treatment are only relative failures with a somewhat prolonged course which, however, does not give rise to anxiety, as there is conjunctivitis rather than purulent ophthalmia. Isolated cases of complete resistance to sulphonamides have, however, been observed. Babies tolerate oral sulphonamides well. Nothing is gained by using doses smaller than those indicated,

and it is important to continue the sulphonamides for forty-eight hours after clinical cure, as the too early suspension of treatment may lead to a relapse.

Penicillin therapy.—Unlike the sulphonamides, penicillin remains effective in the presence of pus. It can therefore be used as a local agent, and has one other advantage over the sulphonamides in that cure is even more rapid and dramatic; treatment, however, is rather exacting. In the use of penicillin, concentration and frequency are all-important. The routine procedure consists of the following stages:—

(1) A swab of the pus is taken for bacteriological examination.

(2) The eye is then irrigated with half-normal saline at room temperature to wash away the pus.

(3) A nurse seated on a chair takes the baby on her lap, and another nurse is responsible for putting in two drops of penicillin, 10,000 units per ml., every minute into the eye.

(4) Pus does not tend to reform while this treatment is in progress. Any secretion formed can readily be wiped off with pledgets of cotton-wool.

(5) Within twenty to thirty minutes the picture is changed. Although the lids are still swollen, and the conjunctiva still remains moist, there is now no tangible secretion.

(6) After thirty minutes of this treatment the baby is returned to his cot. One drop of atropine, 1 per cent., is instilled as a precautionary measure.

(7) Penicillin drops are now continued at five-minute intervals for half an hour.

(8) At the end of this half-hour penicillin is continued at half-hourly intervals for six hours, and subsequently at hourly intervals for twelve hours. By this time the eyes are as a rule normal.

Failures with local penicillin treatment, as with oral sulphonamide therapy, are few. In such cases these two agents may be used in combination.

A striking feature of both sulphonamide and penicillin treatment is their efficiency over the whole range of causal organisms, including the virus of ophthalmia neonatorum. Gonococcal cases respond rather more quickly than non-gonococcal cases to oral sulphonamide treatment, and it is possible that those due to diphtheroids respond rather less readily to local penicillin therapy than the cases due to other organisms. These, however, are minor differences and do not materially affect the dramatic and gratifying response of ophthalmia neonatorum to the modern methods of treatment.

Results reported with the newer antibiotics do not show them to possess any advantage over the standardized procedures with sulphadimidine and penicillin.

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NON-SPECIFIC URETHRITIS

THERE are numerous causes of non-gonococcal urethritis, but the commonest and most important is often called 'non-specific' urethritis because no specific cause has been identified.

CLINICAL COURSE

This condition is undoubtedly a venereal disease, although it may be confused with other and less common conditions which are non-venereal.

In the male it occasionally presents as an acute purulent urethritis resembling gonorrhœa, and there may even be hæmaturia. In most cases, however, it is a low-grade urethritis with onset from ten days to four weeks after intercourse. The discharge is muco-purulent and often scanty. The urine commonly shows threads in the first specimen with the two-glass test; the second specimen is usually clear. Stained smears of the urethral discharge show pus cells and epithelial cells, but no organisms; ordinary cultures grow no organisms—or merely a few contaminants. For this reason an alternative and more satisfactory name for this disease is 'abacterial urethritis'. The condition may prove highly resistant to treatment and may persist indefinitely in latent form, with the possibility of frequent clinical relapses. In some cases there are complications which may be local or metastatic. One characteristic of the urethritis in the male requires special mention. The urethral secretion is sometimes so slight that the patient does not notice it. This probably accounts for the long incubation periods which are sometimes described, for the secretion may be present for some time before it attracts attention. The true incubation period is probably about ten to fourteen days. In other cases the patient may remain quite unaware of his condition, which comes to light in the course of routine examination or through the development of a complication.

In the female, the infection is commonly asymptomatic from the first. If symptoms are present they may be due to associated trichomonal vaginitis. Examination may show urethritis, cervicitis and, perhaps, proctitis. The diagnosis is difficult to make in the female, because the evidence of urethritis is usually slight and the cervicitis has no characteristic features.

Thus, asymptomatic infection is common in both sexes. Those who suffer from it are infectious to others and may at any time develop some complication. When the diagnosis is made or suspected, the partner in marriage and other sexual contacts should always be examined and tested.

LOCAL COMPLICATIONS

These resemble the complications which may result from gonococcal infection, and include prostatitis, epididymitis and cystitis in the male, and pelvic infection and Bartholinitis in the female.

Prostatitis is present in many of these cases and is often established when

the patient is first seen. It is commonly symptomless, and the signs may be minimal and easily overlooked. The diagnosis is usually made after the urethritis has subsided, by the evidence of persisting infection in the patient's early morning urine, and by excess of polymorphonuclear leucocytes in the prostatic secretion. The prostate usually feels normal to the examining finger, but, with long-standing infection, may become abnormally firm and indurated, or show localized areas of induration. The seminal vesicles may also be involved and may show induration.

Epididymitis is usually milder than the equivalent condition due to gonorrhœa. It is uncommon in those cases which are promptly recognized and skilfully treated, but when the original urethritis is missed the condition may present as unilateral epididymitis, which has to be diagnosed from tuberculous epididymitis. The patient complains of pain in the corresponding testicle and, on examination, the globus minor on the affected side is found to be enlarged, tender and indurated.

Bartholinitis due to this cause is not very common. It presents with symptoms and signs resembling those of gonococcal Bartholinitis. It may go on to abscess formation and require drainage.

Pelvic infection.—Ascending infection, with inflammation of the uterine adnexa, occurs in many cases in the female; later, recrudescence and relapse of tubal inflammation are common. Sterility is a possible sequela.

Conjunctival infection of the newly-born (ophthalmia neonatorum) may result from this cause.

METASTATIC COMPLICATIONS

These are more common in the male but may occur in either sex. The commonest complication is arthritis, which may be acute or subacute, usually involves more than one joint and has a special predilection for joints of the lower limbs. The illness which follows may last a few weeks or for many months. It may be relatively slight or very severe and associated with severe toxæmia. The joints usually make a good recovery, even in severe cases, but further attacks of arthritis are common and may ultimately lead to chronic arthritis and painful residual deformities, especially of the feet. There is considerable evidence that this is one cause of ankylosing spondylitis and also of anterior uveitis, which may be associated with arthritis or occur independently. Uveitis is apt to be a recurring condition. During attacks of urethritis, bilateral conjunctivitis may occur, and sometimes there is an eruption on mucous membranes, particularly of the preputial sac (circinate balanitis), and of the skin, particularly the soles of the feet (keratoderma blennorhagica). The triple syndrome of urethritis due to this cause, arthritis and conjunctivitis is often known as Reiter's disease or Reiter's syndrome.

DIAGNOSIS

The diagnosis is made by the clinical evidence, examination of the sexual partner and exclusion of gonococcal infection by bacteriological tests.

Treatment should never be given until the necessary specimens for microscopic smears and cultures have been taken. In the chronic stage in the male, examination for urethral secretion before the first morning urine has been passed and microscopic examination of the first urine are valuable tests. Microscopic examination of the prostatic fluid may be diagnostic.

TREATMENT

The urethritis is apt to be resistant to treatment and is prone to relapse after apparently successful treatment. The evidence suggests that sulphonamides, penicillin, streptomycin and chloramphenicol are ineffective. Lyall (1953) claimed good results by combining streptomycin and sulphonamides. He gave 1 gramme of streptomycin intramuscularly, followed by 6 grammes of sulphathiazole daily for five days, and general experience shows that moderately good results can be obtained with this method. Most of the newer antibiotics are known to have some effect. Harkness (1953) obtained best results with oxytetracycline. He gave 500 milligrams six-hourly for four days, but the results seem to be as good with half the dosage, although most observers prefer to continue treatment for five days. Reasonably good results have also been obtained with similar dosage of chlortetracycline, tetracycline, oleandomycin and spiramycin. Erythromycin also has some effect. There seems little doubt, however, that in many cases there is no form of treatment which is more than suppressive. Some patients still harbour infection and are prone to relapse.

Treatment of the complications is a specialized matter and most of these patients require to be in hospital. Antibiotics seem quite ineffective in the treatment of the metastatic complications, but it is difficult to assess the value of any form of treatment for them, because of the tendency to spontaneous recovery. Good results have been claimed for artificial fever therapy, and steroid hormones have their place, especially in the treatment of the ocular complications.

CONCLUSION

This disease is undoubtedly very common and a major source of ill-health and unhappiness. It has been much neglected in the past but there are signs of awakening interest. It seems unlikely that there will be much progress until the causative organism has been discovered. What is required is intensive bacteriological and virological investigation.

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NOTES AND QUERIES

Surgery in Cerebral Hæmorrhage

QUERY.—What are the indications for surgery in cases of cerebral hæmorrhage?

REPLY.—Surgical treatment for intracranial hæmorrhage is indicated when the patient survives the initial twenty-four hours following the episode and is then left with severe neurological signs with, or without, coma. It is assumed that the term 'intracranial hæmorrhage' is taken to mean hæmorrhage into the striatal region due to cerebral arteriosclerosis. Many other forms of intracerebral bleeding occur and in such cases the treatment will depend upon the cause of the hæmorrhage as, for example, intracranial aneurysm or angioma. These conditions require careful radiological investigation as a preliminary to active surgical treatment.

WYLIE MCKISSOCK, O.B.E., M.S., F.R.C.S.

Hyperidrosis of the Hands

QUERY.—A patient, a girl aged 13 years, suffers from profuse sweating in the hands only, especially in hot weather. Peripheral vasodilators, vitamin A, D and B complex were useless. It was mentioned that 'pro-banthine' might be useful in such cases, and it proved of some value but not completely. I should be pleased if you would guide me to any other better treatment.

REPLY.—Hyperidrosis of the hands is often the reaction of a nervous subject, particularly in adolescence. Probably the best treatment in this child would be 'bellergal', one tablet twice or thrice a day, to diminish her reaction. In addition, she should soak the hands in cold hypertonic saline once or twice a day and, after drying them, apply a saturated solution, or, if this should prove irritating, a more dilute one, of common alum two or three times during the course of the day. This should control the sweating. If this fails, a 3% solution of formaldehyde might be added to the cold saline baths, provided that it does not produce irritation or a tendency to eczema.

R. T. BRAIN, M.D., F.R.C.P.

A Blood Transfusion Problem

QUERY (from a reader in Iraq).—In Cecil and Loeb's 'Textbook of Medicine' (9th edition), on page 1180, it is stated:—'When the donor's blood contains high titres of anti-A or B agglutination as in some samples of group O blood, the transfusion may result in the gradual destruction over days of the donor's red cells carrying the A or B agglutinogen. This difficulty can be avoided by adding A and B (Witebsky) substances to the donor's blood before use, but the doctor should always ask himself "Is the transfusion really necessary?" ' What is the value of these 'A and B (Witebsky) substances'?

REPLY.—There is some ambiguity in the opening sentence of the passage quoted. The serum of group O blood always agglutinates A and B cells suspended in saline, but may do more; for example, it may hæmolyse them. The ability to hæmolyse A (or B) cells is one of the so-called 'immune characteristics' that O serum may manifest, and it is generally believed that it is the presence of such characteristics, rather than the mere ability to agglutinate cells suspended in saline, which renders a serum 'dangerous'. In practice there is a fairly high correlation between high-titre saline agglutinins and the presence of immune characteristics, but there are exceptions, and it is probable that high-titre agglutinins alone are relatively harmless whereas a serum which has only low-titre agglutinins but displays immune characteristics is dangerous. Thus, the first sentence would be more accurate if it said, 'When the donor's serum contains anti-A or anti-B displaying immune characteristics . . .'.

Purified A and B substances (prepared from pig stomach and horse stomach respectively) readily neutralize anti-A and anti-B saline agglutinins but do not readily neutralize the immune characteristics. For this reason they will not make a bottle of O blood really safe for transfusion to an A or B subject if the O blood contains strong immune anti-A or anti-B. Most transfusionists are not content to rely on the neutralizing value of A and B substances but prefer to avoid transfusing O blood to patients of other groups. If O blood must be used, an attempt should be made to select donors whose serum contains not more than a trace of immune anti-A or anti-B.

P. L. MOLLISON, M.D., F.R.C.P.

Undescended Testicle

QUERY.—My son, aged 5 months, has a left undescended testis which I failed to feel through the inguinal canal. Does this mean it is in the abdomen, or is it possible that it is totally absent? Is it advisable to proceed to any hormonal treatment?

REPLY.—It is not justifiable to assume that, because one cannot palpate an undescended testicle, it is in the abdomen. The testis of a five-months-old infant may be very small and if he is a bonny baby the amount of fat in the pubic region may make it impossible to identify the whereabouts of the testicle. It is, of course,

possible that the testis is totally absent, but extremely unlikely. The condition of anorchia is rare.

At the age of five months no treatment at all is indicated, and certainly not hormone therapy which, to be effective—and this would depend on the testis being in the inguinal canal and not in an ectopic position such as the superficial inguinal pouch—might require doses which could lead to undesirable signs of precocity such as growth of pubic hair, acne, or deepening of the voice. For this reason I prefer to undertake hormone therapy, if that is the treatment indicated in any individual case, between the ages of nine and twelve.

PETER BISHOP, D.M., F.R.C.P.

Treatment of Amœbic Hepatitis

QUERY.—Despite the fact that many books state that oral chloroquine is as efficacious in the treatment of amœbic hepatitis as parenteral emetine, many authorities seem to consider that 'to get rid of it once and for all' a course of emetine is essential, suggesting that relapses are more common after chloroquine therapy. Is there any basis for this assumption, as chloroquine is so much more convenient to administer and less toxic?

REPLY.—Infection of the liver by *E. histolytica* manifests itself as amœbic hepatitis or as amœbic abscess, and may occur at the time of, or immediately following, amœbic dysentery but may occur long afterwards. Consequently, whilst amœbæ, trophozoites or cysts may be discovered in the stools, the diagnosis of amœbic hepatitis is not rendered untenable by the failure to find present evidence of bowel infection. Thus, direct evidence of the nature of the infection may be lacking but confirmation of the clinical diagnosis is obtained from the rapid amelioration of the symptoms and reduction of temperature, liver tenderness and enlargement which follow in three to four days the administration by subcutaneous injection of emetine hydrochloride—1 grain (0.6 g.) daily in adults. Emetine injections need not continue for more than four to seven days but as soon as the response mentioned is noticed, chloroquine diphosphate or sulphate may be given orally. The dose is 0.3 g. base thrice daily for two days and 0.15 g. base thrice daily for at least twelve days.

On completion of the course of chloroquine it is wise to give emetine bismuth iodide, 3 grains (0.2 g.) in gelatin capsules nightly for ten nights, to eradicate any amœbic infection in the bowel which must be the source from which liver infection was derived. The failure to demonstrate bowel infection does not exclude the necessity for this step in guaranteeing cure.

Emetine hydrochloride by injection is rapidly absorbed and is active against amœbic trophozoites. Its toxicity has been overestimated. Provided that the patient is kept at rest during treatment, and has no obvious contraindication such as heart disease, a course lasting ten days is quite safe. Dangers occur when such treatment is given to ambulant patients, or when the diarrhœa which is a side-effect of emetine is regarded as evidence that the disease is not responding to the drug and more prolonged dosage schemes are instituted. Chloroquine is concentrated in the liver but this and its relatively slow absorption necessitate a loading dose, and the clinical response, so valuable as confirmation of the diagnosis, is much less obvious than when emetine is used. Relapse of amœbic hepatitis is due either to inadequate therapy to destroy the parasites in the liver, or, probably more commonly, to failure to eradicate an overlooked infection in the bowel.

STANLEY BELL, M.D.

Prednisolone and Insomnia

QUERY.—I had an attack of allergic dermatitis and took prednisolone ('meticortelone'), tablets of 5 mg. four times daily. My last dose was at 8 p.m. Although its effect is wonderful I suffered from insomnia during the five days' course of treatment. I should be grateful if you could tell me whether there has been such a report before.

REPLY.—Although insomnia is not considered to be one of the normal side-effects of prednisolone it does occur in some cases. It is well known that the glucocorticoids may produce a stimulation of the cerebral cortex and frequently euphoria follows their use. In extreme cases mania or other psychotic episodes may occur. It seems likely that the insomnia represents a minor degree of this process.

KENNETH MACLEAN, M.D., F.R.C.P.

Persistent Hot Flushes

QUERY.—I would be grateful for advice on the following case. The patient is a woman, aged 62, who had a thyroidectomy in 1926 and the menopause at about the age of 50, since when she has been bothered with hot flushes. General condition: subthyroid state but has improved with 'eltroxin'.

The flushes do not respond to treatment with stilbœstrol or 'TACE'. They only improve when she is away from home and among strangers. Tonics and reassurance are useless. I have treated her for two years without effect and she is very depressed that neither I nor a specialist can help.

REPLY.—Are these true hot flushes with sweating, or a neurotic or hysterical 'explosion'

against home difficulties? Has she had intermissions? Twelve years of flushes is unusual.

If they are 'true flushes', I should try:—

(a) *Massive doses* of ethinylœstradiol, 0.5 mg. thrice daily for five days, then twice daily for ten days. Then stop. (Uterine bleeding can be discounted, provided it is watched.)

(b) If still active I would try vitamin E ('ephynal'), 1000 mg. daily for twenty-eight days.

If, as seems more likely, they are a hysterical phenomenon, then the treatment is phenobarbitone, and perhaps tiny doses of amphetamine. The subthyroid state is irrelevant.

W. R. WINTERTON, M.B., F.R.C.S., F.R.C.O.G.

Child Adoption

QUERY.—Why do the adoption societies refuse to let families of one sex adopt a child if they can afford to? One of my patients has a family of five girls. Both parents are anxious to adopt a boy, but none of the adoption societies will co-operate.

REPLY.—It is well known that there are far more married couples seeking children for adoption than there are children available. In the circumstances it is understandable that adoption societies have their rules about 'rationing'. It may, however, be possible to find a child through the local authority Children's Officer's department or to hear of a child through various sources such as family doctors, moral welfare committees, hospitals or nursing homes. The law about third-party adoptions must of course be followed, but there is no reason why some sort of 'introduction' cannot be arranged provided that all proceedings are conducted through an adoption society (if they agree) or the local authority.

PROFESSOR ALAN MONCRIEFF, C.B.E., M.D., F.R.C.P., F.R.C.O.G., J.P.

Accidental Exposure to Cæsium-137

QUERY.—In the construction of a pipeline gamma rays are used in the radiography of welded seams to determine the completeness of the union. Recently, despite elaborate precautions, a worker was exposed to cæsium-137 (source = 6 curies) for 15 minutes at a distance of two feet from his abdomen. For ten seconds he actually handled the capsule containing the isotope.

How should such a case be managed? What local and general effects can be expected in this case and for longer periods of exposure to a similar source?

REPLY.—We have done one or two calculations on the data and our estimate of the doses received would be:—

(1) 15 minutes' exposure to the abdomen —2 rads

and (2) 10 seconds' exposure to the palm of the hand—100 rads.

These are no more than estimates, for which a number of assumptions have had to be made. Nevertheless, I believe that they are quite close to the truth. So far as the abdominal dose is concerned, it is of little significance and it amounts to no more than a dose that we would regard as permissible within a period of perhaps two months. It would be quite out of the question to expect that a dose of this size would produce any local or general effects at any time. The skin dose is, of course, much larger but, again, it is unlikely that there will be any effects from it because the skin is considerably less sensitive than many other tissues. If we look at these doses in isolation there is really nothing to recommend in the way of case management, but their real significance, I think, lies in the fact that the repetition of this sort of thing could lead very quickly to serious results. It is of the utmost importance therefore that people who work with sources of this sort should receive very clear instructions and that their work should be under the continuous supervision of someone competent in the field of radiological protection.

ANDREW MCLEAN, M.B., D.I.H.

PRACTICAL NOTES

Iproniazid in Hypertension

THE hypotensive action of iproniazid ('marsilid') has been investigated by G. P. Hallwright (*New Zealand Medical Journal*, June 1958, **57**, 213) in 15 patients, in 14 of whom there was some complicating feature, such as angina pectoris, electrocardiographic evidence of coronary disease or of left ventricular stress, or cerebral vascular disease. The initial dose was 50 mg. thrice daily. Because of side-effects the daily dosage had to be reduced to 100 mg. in six patients at the end of four weeks. During the nine weeks covered by the trial there was an appreciable fall in the mean diastolic pressure in 14 of these patients. The hypotensive action is described as 'smooth and prolonged, reaching its maximum about the fourth week, with an appreciable postural effect'. Euphoria was present in most patients and, 'perhaps at times a little excessive, contributed to a feeling of well-being, a refreshing feature

contrasting with the effects of reserpine and the ganglion-blocking drugs'. Side-effects—dryness of the mouth, constipation, insomnia, loss of sexual capacity, and disturbance of micturition—were frequent but not severe. It is suggested that 50 mg. twice daily would be an adequate dose for many hypertensives.

Triamcinolone in Rheumatoid Arthritis

THE efficiency of a new synthetic corticosteroid (triamcinolone; 'ledercort') in rheumatoid arthritis has been investigated by E. F. Hartung (*Journal of the American Medical Association*, June 21, 1958, **167**, 973). The 'therapeutic results were good' in 16 of 23 patients who had been receiving the drug for periods varying from six to eleven months, and in whom the average duration of the disease was fifteen years. Eighteen of them had previously been treated with prednisone or prednisolone for over a year and in all these side-effects of therapy had been so severe that it had to be stopped. The average dose of triamcinolone necessary to maintain adequate antirheumatic effect was 10 mg. daily in four divided doses. The initial dose was usually around 24 mg. daily. Whilst side-effects, such as rounding of the face, hirsutism and cutaneous purpura, were not uncommon, in no case did œdema or hypertension develop, and the incidence of gastro-intestinal disturbances was much less common and much less severe than with prednisone or prednisolone. Again, unlike other corticosteroids, there was no gain of weight. Indeed with triamcinolone most of the patients lost weight—probably due to water loss, but this was never excessive.

Gold Therapy in Rheumatoid Arthritis

COMPLETE remission in 82.3% of cases is claimed by R. T. Smith and his colleagues (*Journal of the American Medical Association*, July 5, 1958, **167**, 1197) from the use of gold salts in the treatment of rheumatoid arthritis. This satisfactory result is attributed to 'individualization' of the dose for each patient. They report their findings in an investigation of total weekly urinary excretion rates of gold in patients on chrysotherapy, which indicate that variations in patients' response are due to wide differences in the retention and excretion of gold. Details are given of how to adjust dosage to individual requirements and it is said that 'when adequate gold salts are administered on a weekly basis, complete remission can be expected in twelve to eighteen weeks and will be continued by maintenance therapy for eight months'. Toxicity to gold salts is not considered a serious hazard: 'it is reversible and provides a measurement for reinstituting an adequate non-toxic maintenance dose to secure a permanent remission'.

Satisfactory results are also reported by L. Maxwell Lockie and his colleagues (*Ibid.*, p. 1204) from the use of gold: '20% better chance of complete recovery or major improvement'. They analyse their findings in 507 patients who received weekly intramuscular injections, beginning with 10 mg. and working up to 40 mg. Their evidence indicates that more than 300 mg. of gold salts must be given to influence the course of the disease favourably.

Treatment of Choriocarcinoma

'INTENSIVE methotrexate [amethopterin] therapy is a practicable and highly useful form of medical treatment of advanced trophoblastic disease', according to Min Chiu Li and his colleagues (*New England Journal of Medicine*, July 10, 1958, **259**, 66). Amethopterin is a folic acid antagonist. It was administered orally or intramuscularly in a daily dose of 15 to 25 mg. for five consecutive days. No further therapy was given until 'all signs of induced toxicity, such as stomatitis, leucopenia, thrombocytopenia, enteritis and drug rash had in most cases completely subsided'. This usually involved an interval of seven to twelve days. Subsequent courses of five days' duration, with corresponding intervals, were repeated as required, one of the patients in the series receiving a total dose of as high as 1,875 mg. One patient died after the fifth course as a result of jaundice and intestinal ulceration attributed to the drug. The remaining five women remained in remission for periods varying from three to twenty-three months. Two of these women 'present no residual evidence of disease'. The best guide to the efficacy of the drug is a marked drop in the level of urinary excretion of chorionic gonadotrophin. None of the five men with embryonal carcinoma of the testis, who received the same therapy, showed any response.

The 'Crystal' Cervical Test

IF a specimen of mucus from the cervix uteri is spread thickly on a microscope slide and, after drying rapidly over a small spirit lamp, is examined under low-power magnification, a 'beautiful and intriguing crystal pattern resembling fern leaves' may be seen under certain conditions. This appearance only exists during the first phase of the menstrual cycle, when the predominant ovarian hormone is œstrogen. In the second, progesterone-dominated phase it does not occur. This cyclical variation in the crystallization of dried cervical mucus is a constant and reliable finding which, according

to A. D. H. Browne, of Dr. Steevens' Hospital, Dublin (*Journal of the Irish Medical Association*, July 1958, **43**, 211), 'constitutes a simple and definitive test to distinguish the phases of the menstrual cycle' and which will 'almost certainly have an appeal to practitioners in remote places, who have to rely on their own resources entirely'. Its main value is in providing reliable evidence of ovulation, but it is also of value as a pregnancy test in providing a negative answer. Thus, the presence of crystals in a patient who believes she is pregnant justifies the assumption that she is not in this state. There are two conditions which may render results unreliable: the presence of blood in the specimen, and chronic cervicitis.

Intussusception in the Adult

ALTHOUGH primarily a disease of infants and children, over 1,252 cases in adults have been reported in the American and English literature since 1892, according to G. B. Sanders and his colleagues (*Annals of Surgery*, June 1958, **147**, 796). In contrast to children, in whom no specific cause for the intussusception can be found in 95% of cases, 80% of cases in adults are due to some specific organic lesion, 36.6% being due to malignant tumours and 31.3% to benign tumours. In those cases involving only the large bowel and rectum the association with malignancy is even more striking, 62.2% of adult intussusceptions involving the large bowel being caused by, or associated with, a carcinoma. Another difference between children and adults is that in the latter the acute episode leading to surgery is often preceded by intermittent bouts of abdominal cramp over a period varying from days to years. As the incidence of malignant causation is high, it is recommended that a malignant etiology be suspected in the patient over 50. Attention is drawn to the differences between cases due to benign and to malignant tumours. In the latter the duration of symptoms tends to be shorter than in the former, and in between attacks of pain they tend to deteriorate, whereas in the cases with benign tumours the patient feels well in between attacks. Only about one-third of adults with intussusception due to benign or malignant tumours give a history of rectal bleeding or are found to have blood in the stools.

Skin pH in Seborrhœic Dermatitis

'IT is highly probable that seborrhœic patients have generally more alkaline skin surfaces than normal children and that this difference becomes more marked in body areas where clinical manifestation of the disease is present', according to J. Martin Beare and his colleagues (*British Journal of Dermatology*, July 1958, **70**, 233). This conclusion is based upon their findings in an investigation of the pH of the skin surface of 45 children, aged 3 months to 3 years, with seborrhœic dermatitis, and a comparable group of 45 children with healthy skins. They found that the mean pH of 15 of the 16 body sites of seborrhœic children was higher when these sites were affected than would have been expected from the corresponding control observations, and for eight sites the difference was significant (at $P < 0.05$). The mean pH of 12 of the 16 body sites of seborrhœic children was higher when these sites were unaffected than would have been expected from the corresponding control observations, and for three sites this difference was significant. It is suggested that 'the fact that the seborrhœic skin is alkaline may be the underlying reason why these patients so often show surface infection of one kind or another'.

Trichobezoars

TRICHOBEZOARS are not common. According to C. S. Hoyt *et al.* (*Proceedings of the Staff Meetings of the Mayo Clinic*, May 28, 1958, **33**, 298), in reporting the first case to be seen at the Mayo Clinic since 1950, the sum total of cases reported in the literature is now 230. Their case is that of a girl, aged 10½ years, who, at a routine school medical examination, was found to have a palpable mass in the upper abdomen. There was a history of chewing hair on and off since infancy. Otherwise she was a normal child, and even the psychologists had to admit that she was 'an unusually sociable, talkative and self-reliant youngster who showed no evidence of the hostile, incorporative drive often seen in patients with trichotillomania'. At operation an 'extremely firm' trichobezoar measuring 18 x 10.5 x 6 cm. and weighing 560 grammes, which had formed an entire cast of the stomach, was removed. It lay loose in the stomach and was easily removed. The postoperative course was uneventful. From a review of the literature it is noted that the condition is extremely rare in males and that more than 80% of cases have been diagnosed before the age of 30. The largest so far reported weighed 2.95 kg. The diagnostic triad is a history of hair swallowing, a palpable epigastric mass, and radiological demonstration of the condition by means of a barium meal. Not infrequently, hairs may be found in the stools.

Curly Toes

CONGENITAL deviation of the third and fourth toes, usually referred to as congenital curly toes, is a common condition. In some instances the second toe is also involved. The deformity is a mixture of adduction and flexion, mainly at the terminal joint, but also in the proximal joint. In the more severe cases this is combined with

rotation of these joints, the nail coming to lie towards the lateral side. Both feet are often involved. R. Sweetnam (*Lancet*, August 23, 1958, **ii**, 398) has investigated a series of 50 cases, 21 of which had been treated and 29 left untreated. Treatment consisted of attempted correction by means of over- and under-strapping for many months, the average being thirteen months. In only three children was this treatment initiated after the age of two years. All the children were seen again in adolescence —the average age at re-examination being 13. At the follow-up the number showing improvement was approximately the same in the two groups: 25% of the treated group and 27% of the untreated group. In no foot, treated or untreated, was any deterioration found in the deformity, and none of the children examined had any symptom attributable to the condition. In other words, over- and under-strapping has no significant effect on the outcome of the deformity. Further, 'since a quarter of the untreated cases improved and none of the remainder deteriorated, it is doubtful whether any form of treatment is worth while'.

Desensitization to PAS

FOUR cases of hypersensitivity to PAS, in which desensitization was rapidly and satisfactorily induced by corticotrophin are reported by R. S. Francis and S. K. Gupta (*Tubercle*, August 1958, **39**, 236). Desensitization was achieved in six days in three of the cases and in four days in the other. Details of one of the cases are as follows:—

> On September 17, the patient developed a severe rash with slight pyrexia. All drugs (i.e. streptomycin, PAS, isoniazid) were discontinued and antihistamines were prescribed. On September 19, 90 mg. of corticotrophin suspension were given in divided doses, and administration of all antituberculous drugs was reinstituted. As the rash persisted, on September 20 the dosage of corticotrophin was increased to 140 mg., then reduced daily to 90 mg., 45 mg., 25 mg., and nil. The rash cleared by September 22 and treatment was continued in the ordinary way without any further complications.

The following are among the advantages claimed for this method of desensitization. 'It is not necessary to wait for symptoms to subside before giving corticotrophin; patients may continue effective chemotherapy within a few days of the onset of hypersensitivity, and desensitization is usually completed within the following week. Symptoms are rapidly relieved and the patients' morale is minimally disturbed. There are no grounds for fearing the development of bacterial resistance, and the side-effects of prolonged corticotrophin treatment are avoided'.

Coronary Heart Disease and Occupation

FURTHER evidence that coronary heart disease is not as uncommon among agricultural workers as some would make it out to be is reported by A. C. Kennedy and Betty Cowan (*Scottish Medical Journal*, July 1958, **3**, 283). In a random sample of 96 men, aged 55 to 64, in a rural area in South-West Scotland, 43 (44.8%) were actively engaged in agriculture. Twenty-three (24%) of the entire series had evidence of coronary heart disease, and eight (35%) of these were agricultural workers. Other points brought out in this survey are that there was no difference between the smoking habits of the coronary and the non-coronary groups, that the average weight of the coronary group was 167.5 lb. (76 kg.) compared with 155.6 lb. (70.6 kg.) for the non-coronary group, and that the mean blood pressure of the coronary group was 159.9/96.5 mm. Hg, compared with 162.9/95.3 mm. Hg for the non-coronary group. It is also noted that 'no evidence is forthcoming from the present investigation that heavy physical work appears to have a protective influence against the development of coronary heart disease'.

Tuberculosis and Peptic Ulcer

EVIDENCE indicating a higher than average, significant occurrence of peptic ulcer in tuberculous patients is adduced by D. M. Kissen (*Health Bulletin*, July 1958, **16**, 44). Among the 829 patients attending his tuberculosis follow-up clinics during 1956 there were 34 (4.1%) with peptic ulcer. In 15 cases the peptic ulcer occurred before, and in 15 cases after, the onset of the tuberculosis. In the remaining four the onset of the two conditions was so close to each other that it was impossible to say which came first. Of the 15 patients in whom the peptic ulcer preceded the tuberculosis, the former had been treated surgically in seven cases, the remaining eight being treated medically. Of the 15 in whom the peptic ulcer followed the tuberculosis 11 had been medically treated. The average time by which the ulcer preceded the tuberculosis was 7.9 years (range, 3 to 21 years). The comparable figures for the post-tuberculosis ulcer group were 7.3 years (1½ to 11 years). The view is expressed that 'the finding of as many patients developing their ulcer after pulmonary tuberculosis as before it, especially with such long intervals between . . . is not in keeping with the theory that the malnutrition of peptic ulcer is a main factor in the association of these two conditions. Nor does the finding of more ulcer patients having had medical treatment than surgical . . . support the view that surgical treatment . . . predisposes to the development of tuberculosis'. As an alternative he suggests that 'the association between the two conditions can be better understood if it is appreciated that both have a psychological basis in their etiology'.

REVIEWS OF BOOKS

System of Ophthalmology. Vol. I, *The Eye in Evolution*. Edited by SIR STEWART DUKE-ELDER, G.C.V.O., M.D., D.SC., F.R.C.S. London: Henry Kimpton, 1958. Pp. xvi and 843. Figures 902. Plates xiii. Price £6 6*s*.

TECHNICALLY this is the first volume of the second edition of the editor's 'Textbook of Ophthalmology'. In practice it is a new book. The Textbook, universally acclaimed as the leading authority on the subject, appeared in seven volumes and was entirely the work of Sir Stewart Duke-Elder. The new edition is to be published in fifteen volumes and for this monumental undertaking the task of rewriting is being shared with the editor's colleagues at the Institute of Ophthalmology.

The first volume, however, has been written in its entirety by the editor. It is a magnificent *tour de force*. As the author points out, the subject-matter has never been gathered together in one volume, but it is much more than a mere encyclopædia. It is a brilliant exposition of the subject written with a clarity and felicity of style which will prove irresistible to the discriminating reader. This is no dry-as-dust tome for the pedant—much as he will learn from it—it is an enthralling tale told with consummate skill. It will be essential reading for every ophthalmologist, but no practitioner interested in natural history can afford to miss it. The illustrations—there are well over 900 of them—are chosen with the same skill as that with which the book is written. The doctor who does not beg, borrow, or buy a copy of this book is depriving himself of hours of sheer joy—and the reviewer knows of no other 'textbook' of which this can be said. If the remaining fourteen volumes maintain the standard of this one, then British ophthalmology will have made an outstanding contribution to medical literature.

Drugs of Choice, 1958-59. Edited by WALTER MODELL, M.D. London: Henry Kimpton, 1958. Pp. 931. Figures 18. Price 95*s*.

IN the preface this book is described as 'a volume of expert opinion designed to provide the American physician with a comprehensive source of clear, concise, authoritative and practical answers to the continually recurring question of which drug in a rapidly changing scene is, at the critical moment, the drug of choice for an actual therapeutic problem'. For this purpose he has collected a team of thirty-six contributors, which includes many of the leading names in American medicine: Dameshek, Karnopsky, Chester S. Keefer, Marion B. Sulzberger, and John H. Talbott.

The plan of the book is that each chapter is devoted to 'the choice of drugs' for some particular purpose: e.g. for cancer, for hypertension, for disturbances in equilibrium. This arrangement is not without its drawbacks, but for the experienced clinician these are outweighed by the advantages. The expert may be disturbed by some of the dogmatic statements that are made but for the practising clinician a modicum of dogmatism is essential in these days when new drugs pour forth from the pharmaceutical mill every day. A useful feature of the book is the 'drug index' at the end of each chapter, but it is unfortunate that an anglicized version of this has not been provided for the British reader.

Lectures on the Scientific Basis of Medicine. Vol. VI: 1956-57. London: University of London, The Athlone Press, 1958. Pp. ix and 393. Illustrated. Price 45*s*.

THE twenty-one lectures in this volume—selected from the annual course of lectures planned by the British Postgraduate Medical Federation—maintain the high standards of their predecessors. Some—such as Miss Honor Fell on 'The physiology of skeletal tissue in culture', McIlwain on 'Neurochemistry', and Long on 'Phospholipids'—are primarily of academic interest. Others—such as Keele on 'Causes of pain', Sinclair on 'Essential fatty acids in nutrition and their relation to other vitamins', and Seddon on 'Poliomyelitis'—are of more practical interest. All, however, are of interest to the clinician who wishes to keep in touch with current trends in medical research. From the opening chapter by Sir John Cockcroft on 'The biological significance of atomic energy' to the concluding one by K. M. Smith on 'The electron microscope in the study of viruses' this is a magnificent tribute to the high standard of medical research in this country and well repays careful study by the clinician who wishes to retain an intelligent interest in the art and science of medicine.

The Neurological Basis of Behaviour. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.B., B.CH., and CECILIA M. O'CONNOR, B.SC. London: J. & A. Churchill Ltd., 1958. Pp. xii and 400. Illustrations 109. Price 52*s*. 6*d*.

THIS latest addition to the now well-established Ciba Foundation Symposia contains the proceedings of the symposium held last year to

commemorate the centenary of the birth of Sir Charles Sherrington. Whilst primarily a work for the expert, there are many chapters that will prove of interest to the general physician: J. C. Eccles on 'The behaviour of nerve cells', for instance, or C. P. Richter on 'Neurological basis of responses to stress', J. D. Green on 'The rhinecephalon' or J. Elkes on 'Drug effects in relation to receptor specificity within the brain'.

The no-man's land between neurology and behaviour is one of the most fascinating facets of medical research at the present moment, and it is inevitable that this symposium raises as many problems as it solves. As Lord Adrian points out in the final discussion: 'I don't think anyone would be bold enough to bet on the best direction to go or where we should be five years hence: we shall obviously be very much further forward. But forward in what direction or in how many different directions is anybody's guess'. Meanwhile, however, there is ample food for thought in this authoritative review of the position today.

Amphetamine Psychosis. By P. H. CONNELL, M.D., D.P.M. London: Chapman and Hall, 1958. Pp. 133. Illustrated. Price 21*s.*

THIS interesting and scholarly monograph is based on a London University M.D. thesis. Forty-two cases of psychosis associated with amphetamine usage are reported and the conclusion reached, on good evidence, that psychosis due to amphetamine usage is not uncommon. A paranoid psychosis in a setting of clear consciousness is produced and the mental picture may be indistinguishable from acute or chronic paranoid schizophrenia, or from alcoholic psychosis in a withdrawal phase. Patients with amphetamine psychosis recover within a week of withdrawal of the drug unless symptoms are prolonged in hysterical fashion or there is evidence of continued excretion of the drug. The author emphasizes the necessity of using his modified biochemical test (described in critical detail) to differentiate this kind of paranoid reaction from others, and to detect it in patients who deny using the drug. He also emphasizes the high relapse rate due to the severity of addiction to amphetamine and describes apparently normal and well-adjusted individuals who developed this reaction as well as the high incidence of abnormal personality and instability together with alcoholism or other drug addictions in many patients developing this condition. In some, risk of suicide in the withdrawal phase is definite. Connell's adaptation of a clinical test for the determination of amphetamine and its relatives in biological fluids is an important part of the monograph which throughout, both in content and discussion and also in its format, does credit to the Maudsley Hospital and the publishers.

Family practitioners should be aware of this further important evidence of the dangers of ill-considered use of amphetamine, a drug far more dangerous and less valuable than is generally realized. That some of the patients obtain amphetamine by inhalation or from swallowing the contents of inhalers does not lessen the need for critical consideration before this drug is prescribed.

Cancer. Volume III. Edited by RONALD W. RAVEN, O.B.E., T.D., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1958. Pp. viii and 510. Figures 165. Price 85*s.*

THE third volume of this work is divided into five parts dealing respectively with additional pathological aspects, the geography of cancer, occupational cancer, cancer education, and cancer detection. It is a somewhat disappointing sequel to the first two volumes, suggesting that the editor has thrown his net too wide, thereby making the work too superficial for the expert, whilst there will be few but the expert who will wish to expend the requisite sum on a work of this size. Indeed this is almost a perfect example of too many cooks spoiling the broth. Was it really necessary, for example, to get eight individuals drawn from six different countries to cover the geography of cancer? Again, surely cancer education could have been adequately covered in one chapter—rather than the four devoted to it. To British readers it is disconcerting to find that the name of Lindgeon is not even mentioned in the cytodiagnosis of carcinoma of the lung.

For the information which it contains, however, it will prove a useful reference book.

Principal Infectious Diseases of Childhood. By NELLES SILVERTHORNE, M.B. Toronto: University Press; London: Oxford University Press, 1958. Pp. ix and 102. Price 28*s.*

THIS is a brief account of a mixed bag of disorders in childhood, including the more generally accepted specific fevers but extending its range to include even such entities as inanition fever in the newborn and, in a section on virus diseases, warts and homologous serum jaundice. The facts are clearly stated under the conventional headings of etiology, clinical aspects, complications and so forth, and treatment is well set out in a dogmatic fashion very suitable to the type of reader for whom the

book is intended—general practitioners and students. It is a little difficult to understand how selection has been made, for, judging by other topics included, there might well have been more on tuberculosis (meningitis is included) and even a short section on erysipelas and on boils. There are no illustrations and no index.

Non-Venereal Syphilis: A Sociological and Medical Study of Bejel. By E. H. HUDSON, M.D., D.T.M. & H., F.A.C.P. Edinburgh: E. & S. Livingstone Ltd., 1958. Pp. viii and 204. Figures 81. Price 30*s*.

DR. HUDSON was the first to describe the particular form of treponematosis known as bejel and his experience covers twelve years in Deir-ez-Zor from 1924 and a subsequent investigation of the disease in Iraq during 1949 and 1950 under the auspices of the World Health Organization. He does not give the impression of one who has a deep knowledge of the treponemal diseases, but he is an experienced physician and close observer, whose clinical descriptions are evidently the result of detailed study and accurate observation. His account of the disease is reinforced by many excellent photographs. One point requires clarification. The author's comments on some of the photographs seem to suggest that bejel causes true curvature of bones. If this disease is syphilis or closely related to it, that would be very surprising because syphilis, as we know it in this country, strengthens rather than weakens the long bones and the appearance of bowing which is sometimes seen is the result of localized thickening and not of true bending. Dr. Hudson takes the view that syphilis in its venereal and non-venereal forms is the same disease; that it did not first appear in Europe in the fifteenth century but is as old as history, having its origin in central Africa in the disease we now know as yaws. Whether or not this view is accepted the argument is full of interest and the description of this non-venereal treponematosis in its characteristic habitat makes instructive and entertaining reading.

Diagnostic Medical Parasitology. By EDWARD K. MARKELL, PH.D., M.D., and MARIETTA VOGE, M.A., PH.D. Philadelphia and London: W. B. Saunders Co., 1958. Pp. x and 276. Figures 115. Price 49*s*.

THE authors have avoided unnecessary detail in this clear and pleasantly written account of the common protozoal and helminthic parasites of man and of the effects which they produce in the host. As the title of the book suggests, the subject is approached from the practical, diagnostic point of view, and a full description of the standard techniques is given. Any discussion of treatment is deliberately excluded. The numerous photographic illustrations are of excellent quality, though the magnification is seldom stated. The line-drawing of *Microfilaria malayi* in fig. 87 is wrong. No mention is made of *Mf. streptocerca* which is of some importance in Africa, if only because of its possible confusion with *Mf. volvulus*. On the other hand, half a page is given to *Dioctophyma renale*, though it is doubtful if any living parasitologist has seen a case of human infection with this worm. These are very minor adverse criticisms of a book which contains much more to praise than to blame, and it is a pleasure to recommend it as an excellent introductory text or laboratory manual for students of medical parasitology.

The Surgeon's Tale. By ROBERT G. RICHARDSON, London: George Allen & Unwin Ltd., 1958. Pp. 256. Illustrated. Price 25*s*.

THIS is not, as the author suggests in his preface, a book for the layman, but it is an excellent one for the medical student. Indeed no better introduction could be thought of for the preclinical student about to embark upon his clinical career. Unlike so many books on the subject it is selective and correlates the past with the present. This is its distinctive feature and what makes it predominantly a book for the budding clinician—and there are few registrars and practitioners who will not find it a fund of fascinating information. Its other distinctive feature is the stress which it rightly places upon the vitalizing impact of the last two World Wars on surgical practice.

This is no dry-as-dust tome for the armchair historian. It is a brilliantly vital exposition of the living art of surgery which no young practitioner of that art can afford to ignore.

NEW EDITIONS

The Principles and Practice of Medicine, by Sir Stanley Davidson, M.D., F.R.C.P.ED., F.R.C.P., and the Staff of the Department of Medicine, University of Edinburgh, and associated Clinical Units, in its fourth edition (E. & S. Livingstone Ltd., 35*s*.) must be near breaking, if it has not already done so, all records for medical textbooks. Four editions and three large reprints within six years, a Spanish edition, and 'phenomenal demands' from the Commonwealth, the United States of America and 'other parts of the world'. These are but some of the claims which the editor is able to make in the preface to this new edition. When it is added that, in spite of added material, the book is actually smaller than the previous edition, and

it is sold at the same price, then there is really nothing that a reviewer need add. The customer is not necessarily always right, but in this particular instance a large proportion of the student body throughout the world has very quickly tumbled to the fact that here is an introduction to the practice of medicine which is second to none.

Diseases of the Liver and Biliary System, by Sheila Sherlock, M.D., F.R.C.P., second edition (Blackwell Scientific Publications, 57*s.* 6*d.*).—Although it is only three years since the first edition of this book appeared, several sections have been rewritten and much new material has been added. A new chapter is devoted to jaundice and there is an excellent account of hepatic coma and its treatment. Subjects of topical interest include the indications for intravenous cholangiography and splenic venography, the complications of virus hepatitis and the role of auto-antibodies in the etiology of adolescent cirrhosis. A new classification of cirrhosis is given. The author deserves great credit for producing a second edition which is no longer than the first. The book is well written, pleasantly produced and is certainly the most readable and reliable book on this subject in the English language. Liver damage following mushroom poisoning (*amanita phalloides*), however, is not due to muscarine but to amanitine, a quite different toxic substance.

Systemic Ophthalmology, edited by Arnold Sorsby, in its second edition (Butterworth & Co. (Publishers) Ltd., £5 5*s.*), has been thoroughly revised. The general arrangement of chapters has not been altered, but the presentation has been greatly improved by the assembly of the references at the end of the volume. There has been a reduction in the number of coloured illustrations and this is particularly unfortunate in relation to ophthalmoscopic conditions but, in other respects, the book follows the same pattern as before. The contributors have maintained a sensible balance between information useful to the general physician and the specialist. There are many conditions which will rarely be seen by the general practitioner. It will be of particular value to students preparing for higher diplomas, and can be strongly recommended for this purpose.

Lumbar Disc Lesions, by J. R. Armstrong, M.D., M.CH., F.R.C.S., in its second edition (E. & S. Livingstone Ltd., 45*s.*), is an important book. In the foreword it is stated that the book portrays the views of contemporary British orthopædic surgeons, and this it does clearly and precisely. Orthopædic surgeons bear a heavy responsibility to patients complaining of backache and sciatica. They must be familiar with all aspects of the lumbar disc lesion story. Few of us can fail to learn a great deal from this highly informative book that is well written and illustrated. One may, however, get the impression that the author is spinning out his theme a bit. The reader may lose his way in the fifty-seven pages on differential diagnosis. Does the author believe in lumbar fibrositis and primary sciatica? If so, who is he kidding? Not himself, we hope. It would have been to the advantage of the reader if, in writing this section, the author had used his undoubted authority to guide us more clearly from the pitfalls of traditional differential misdiagnosis. Essentially, however, this is a logical and interesting book, and if general practitioners can make time to read it, their patients will benefit from the informed and convincing advice they will be able to give.

Anatomy and Physiology for Nurses, fifth edition, by W. P. Gowland, M.D., F.R.C.S., and John Cairney, M.D., D.SC., F.R.A.C.S. (Christchurch, New Zealand: N. M. Peryer Ltd.; London: Lloyd-Luke (Medical Books) Ltd., 45*s.*). — There is a tendency in modern medical teaching to discard the boundaries, so long regarded as conventional, between individual subjects. For the student, whether nursing or medical, such co-ordinated study results in a more ready assimilation and understanding of the organ and its function. In this edition the authors have performed such a service and must be congratulated on producing a nursing textbook as attractive as has ever been written. The subject material is presented in remarkable detail, and is concise, well tabulated and attractively illustrated. It reads easily and instructively, and more like a tale which unfolds itself than as a standard textbook. For the student nurse it will be valuable for reference in her later medical and surgical studies, a purpose which the authors obviously had much in mind in the compilation of this edition. This book merits, and will achieve, wide recognition and a place, not only in its native Australasia, but in the nursing libraries of the English-speaking world.

The contents of the November issue, which will contain a symposium on 'Radiation Hazards', will be found on page A 142 at the end of the advertisement section.

Notes and Preparations see page 541.
Notes from the Continent see page 545.
Fifty Years Ago see page 547.
Motoring Notes see page A 97.
Travel Notes see page A101.

NOTES AND PREPARATIONS

NEW PREPARATIONS

'ATURBANE' tablets each contain 5 mg. of α-phenyl-α-(diethylaminoethyl)-glutarimide hydrochloride and are intended for the treatment of Parkinsonism. This drug is 'a potent anticholinergic', acting mainly on the brain stem, which 'relieves rigidity, improves mobility, lessens tremor and reduces salivation'. It is said to be well tolerated and 'side-effects rarely interfere with treatment'. Available in containers of 25, 100 and 500. (Ciba Laboratories Ltd., Horsham, Sussex.)

'ENERIL' is described as 'a new anti-pyretic-analgesic elixir', each 4 ml. of which contains 120 mg. of paracetamol. It is said to be free from gastric irritation and readily acceptable to children and 'is recommended as a suitable variant of acetylsalicylic acid mixtures which must be freshly prepared and deteriorate rapidly'. Available in bottles of 4 and 40 fluid ounces. (A. & G. Nicholas Ltd., Slough, Bucks.)

'MEGOBAR' tablets each contain 30 mg. of phenobarbitone and 3 mg. of 'megimide' brand of bemegride and are intended for general sedation. Issued in bottles of 100. 'PHENAGLATE' capsules each contain 50 mg. of quinalbarbitone sodium, 25 mg. of phenobarbitone and 7.5 mg. of 'megimide' brand of bemegride and are intended for medium-acting routine hypnosis. Issued in bottles of 30. The incorporation of bemegride with barbiturates 'significantly modifies the usual toxic manifestations of overdosage of barbiturates whether from accident or intent while preserving the major therapeutic actions of the barbiturates'. (A. & G. Nicholas Ltd., Slough, Bucks.)

'V-CIL-K SULPHA' tablets each contain 125 mg. of penicillin-V potassium and 0.5 g. of sulphadimidine, and are intended for the treatment of 'otitis media, bronchitis, and other mixed respiratory infections, and urinary infections'. Available in bottles of 20, 100 and 1000. (Eli Lilly & Co. Ltd., Basingstoke, Hants.)

PHARMACEUTICAL NOTES

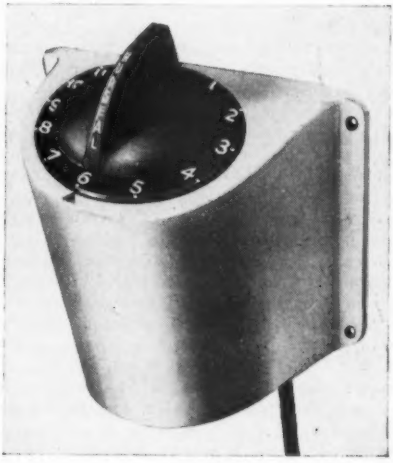
BOOTS PURE DRUG CO. LTD. announce that their range of neomycin preparations will in future be marketed under the name 'nivemycin'. There are two additions to the range: tablets containing 0.5 g. (bottles of 20), and a non-greasy lotion containing 0.5% neomycin sulphate B.P. (plastic applicator-bottles of 1 fluid ounce).

The same company also announce that 'calcipen-V suspension (forte)' has been added to their range of penicillin-V (phenoxymethylpenicillin) preparations, in bottles of 60 ml., each 5 ml. of which contains 250 mg., with plastic spoon. (Station Street, Nottingham.)

THE DISTILLERS CO. (BIOCHEMICALS) LTD. announce that 'distaquaine' V-K scored tablets are now available in an additional strength (60 mg.). (Broadway House, The Broadway, Wimbledon, London, S.W.19.)

NEW APPARATUS

THE 'HURSEAL TIME-SWITCH' is designed primarily to operate with oil-filled electric radiators but may be connected for either lighting or heating or for both simultaneously. It will control up



to 15 amp. on a 12-hour cycle and can be screwed permanently to the skirting board adjacent to the plug it is to control. Among the suggested uses are the pre-heating of bedroom, bathroom, living room or kitchen in the early morning. (Hurseal Ltd., 229 Regent Street, London, W.1, price £2 19s. 6d.)

'SERALETS' are small, sterile, disposable, stainless steel lancets which are 'ideal for producing a drop of blood from a finger because the point is sharp, broad and strengthened, but yet they will cut well enough and deeply enough for a vaccination'. 'Seralets' are each wrapped separately and are supplied in boxes of 250 and envelopes of 20. (Cuxson, Gerrard & Co. Ltd., Oldbury, Birmingham.)

FORTHCOMING CONFERENCE

Factors in the Assessment and Education of Cerebral Palsied Children will be the subject of a conference to be held by the British Council for the Welfare of Spastics on Saturday, November 8, 1958, at The Engineering School, University Walk, Bristol. The conference is being sponsored by the Department of Child Health, Bristol University, who have arranged the programme, and the Chairman will be Professor A. V. Neale. The conference is open to members of the medical profession, and full details may be obtained from the Secretary, British Council for the Welfare of Spastics, 13 Suffolk Street, Haymarket, London, S.W.1.

PRIZES AND SCHOLARSHIPS

THE Council of the British Medical Association announces the following prizes and scholarships:—*Sir Charles Hastings and Charles Oliver Hawthorne Clinical Prizes* (£75 and £50) for the best entries based on systematic observation, research and record in general practice. Closing date for entries is December 31, 1958.

Provisionally Registered Practitioner's Prize (£50) for the best essay on 'To what extent are experiments on animals essential for medical progress?'. Closing date for entries is January 31, 1959.

Medical Students' Prizes (£25 each) for the best essays on 'The Playing Field is a better place than the Library for a Medical Student's spare time in the preparation for his life's work'. Closing date for entries in January 31, 1959.

Scholarships in Aid of Scientific Research (Ernest Hart Memorial Scholarship, £300; Walter Dixon Scholarship, £300, and four ordinary scholarships, £200 each) will be awarded to candidates recommended by the Science Committee of the Association as qualified to undertake research in any subject (including State Medicine) relating to the causation, prevention or treatment of disease. Applications are also invited for the Insole Scholarship (£250) for research into the causes and cure of venereal disease. Closing date for entries for scholarships is March 1, 1959.

Further details of these awards may be obtained from the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

FILM NEWS

Lifting Patients (16 mm., sound) is in two parts: *Part I.—In Hospital* (running time 13 minutes) has been made primarily for showing to nurses, midwives, nurses in training and nursing auxiliaries, and first demonstrates diagrammatically the effect on the body of good and bad lift. Two basic ways of lifting are then shown. *Part II.—In the Home* (running time 11 minutes) is intended primarily for district nurses, health visitors and others engaged in domiciliary nursing but would also be useful for relatives who are nursing patients at home. Part I is designed to be shown alone, but Part II should, if possible, be preceded by it because of the diagrammatic sequence on the physiology of good and bad lifting. These are excellent films which should do much to help in the prevention of spinal injuries to nurses caused through incorrect methods of lifting. Produced for the Ministry of Health by Kinocrat Ltd. and the Central Office of Information, the films can be hired from the Central Film Library, Government Building, Bromyard Avenue, Acton, London, W.3, from whom full details may be obtained.

Causes of Fire, *Action in Case of Fire*, and *Evacuation of Patients* are coloured 16-mm. filmstrips produced by the Departments of Medical Illustration of the South Manchester Hospital Group and the Manchester Royal Infirmary, in cooperation with the Fire Protection Department of the City of Manchester Fire Brigade, at the request of the Institution of Fire Engineers. They are intended for the training of nursing staff, and the lecturer's notes accompanying the strips enable a non-technical lecturer to deal with the subject adequately. Available for use in hospitals and by medical staff generally upon application to The Institution of Fire Engineers, 94 Southwark Bridge Road, London, S.E.1.

The Pfizer Medical Film Programme, which is being launched this autumn, is intended primarily to provide general practitioners with up-to-date information on advances in treatment and diagnosis. Showings are to be arranged throughout the country. Thereafter, the films will be available on loan to hospitals, medical schools or branches of the British Medical Association. Full details can be obtained from Pfizer Ltd., Folkestone, Kent.

ROYAL SOCIETY OF MEDICINE

THE next meeting of the Section of General Practice will be held at 8.15 p.m. on October 15, when the valedictory address on 'Anæsthesia in a Dental Surgery' will be given by Dr. G. M. Kerr. The discussion will be opened by Mr. Charles King.

THE MEDICAL OFFICER

WITH its issue dated September 5, *The Medical Officer* attained its golden jubilee. As the only weekly periodical in the world for public health readers it has long enjoyed a high reputation in

journalistic circles for the quality of its articles and its lively commentaries on matters of interest to those concerned with the health of the community. As it sets forth on its second half century it carries with it the good wishes of all its many friends—and these are to be found in a much wider circle than the public health services.

A SILVER JUBILEE

WE offer our congratulations to the *Indian Journal of Pediatrics*, the first pædiatric journal to be published in India, on attaining its silver jubilee. The articles in the special number published to commemorate the occasion cover a wide range of subjects, including undergraduate and postgraduate training in pædiatrics. Sir Robert Hutchison, who contributed a message to the first issue of the journal, which is reproduced in the silver jubilee number, contributes a special message to this commemorative number in which he says that the journal 'has amply fulfilled the expectations with which it was started and is doing much to encourage the study of pædiatrics in India'.

MORTALITY IN 1957

IN 1957, there were 6,715 deaths from influenza in England and Wales, compared with 2,626 in 1956 and 2,983 in 1955. Deaths from poliomyelitis totalled 225, compared with 114 in 1956 and 241 in 1955. There were two deaths from smallpox, the first in this country since 1953 when there were eight. Deaths from coronary heart disease are still mounting: 70,597 in 1955, 74,790 in 1956, and 76,321 in 1957.

PENSIONS AND NATIONAL INSURANCE

AT the beginning of this year the over-all cost of social service benefits being paid by the Ministry of Pensions and National Insurance was at the rate of £1,080 million a year, comprising about £1000 million for war pensions, about £120 million for family allowances from Exchequer Funds and about £860 million in benefits from the two National Insurance Funds. Contributions being paid by insured persons and employers to the National Insurance and Industrial Injuries Funds were at the rate of £780 million a year, excluding contributions to the National Health Service. The cost of death grants for the year ended March 31, 1957, was nearly £3½ million.

THE RETREAT, YORK

THE report of the Physician-Superintendent for the year 1957 reveals that as a result of reserpine therapy and the consequent reduction in the number of patients needing insulin coma treatment it has been possible to discontinue the special 'insulin unit' and utilize the accommodation as a small senile annexe for elderly women patients. Group psychotherapy was used more widely during the year and in suitable cases the administration of lysergic acid diethylamine shortened the stay in hospital quite considerably 'by seeming to increase the patients' capacity for recall of past important episodes, and it also seems to enable the patient to develop insight and understanding of the mental mechanisms involved more quickly'.

MANCHESTER INFANT MORTALITY

A DISTURBING feature to which Dr. Metcalfe Browne, the medical officer of health for Manchester, draws attention in his annual report for 1957 is the rise for the second year running in the infant mortality rate in Manchester 'whilst contemporaneously the corresponding rate for England and Wales has fallen and in 1957 reached an all-time low at 23.0 per thousand live births'. In Manchester it was 30.10. Two factors are held mainly responsible for this unfortunate state of affairs. There is 'a grave shortage of antenatal and maternity beds': in 1957 the percentage of births in institutions fell to 60%. The second factor is that housing conditions are 'notoriously bad'. To meet the current need of 83,000 houses, 1,894 were built in 1957. Dr. Metcalfe Browne adds: 'Meanwhile Manchester babies will die as a direct result of the poor conditions in these damp defective dwellings'.

EAT LESS AND GROW SLIM

THE only way to lose weight is to eat less, according to the United States Congressional sub-committee which has been investigating the sale of slimming preparations in the United States. 'The American consumer', it declares, 'is being bilked out of approximately $100 million it spends annually on these preparations', and it calls upon Federal Agencies to 'crack down on alleged weight-reducing remedies'.

PUBLICATIONS

John Wesley among the Physicians, by A. Wesley Hill, M.B., B.CH., is a little gem. It sketches the times when medicine was emerging from the long night of obscurantism into the dawn of rationalism, and shows that John Wesley's 'Primitive Physick or an Easy and Natural Way of curing Most Diseases', with its earthy common sense and hygiene, and twenty-three editions in his own lifetime, did much to quicken the process. The only lethal parts of the book are some prescriptions of reputable physicians which Wesley felt bound to include. Wesley was also a pioneer in the medical use of electricity, and his book, 'Desideratum', deals with that subject. But it is as a pioneer psychosomatologist that

Wesley stands supreme: in his recognition of the fact that peace of mind is the greatest healer, in his abreactive methods of getting that peace of mind in serious cases, in the tranquillizing, stabilizing and fortifying influence which he and his followers have had for two centuries on large numbers of their fellow men and women throughout the world. (The Epworth Press, price 10*s*. 6*d*.)

Ward 4, by J. H. Means, M.D., is the history of the famous ten-bedded research ward in the Massachusetts General Hospital, Boston, founded by Professor Means in 1925. Here the author did much of his outstanding work on the thyroid, Aub his brilliant work on lead poisoning, and Allbright his pioneer work on the parathyroids. Harvard is rightly proud of this microcosm of medical research, and no-one was better qualified to undertake the task of writing its history than Professor Means. The book is written primarily for the American layman, but all friends of Boston will enjoy browsing through its pages. (Harvard University Press; London: Oxford University Press, price 36*s*.)

Classification of Atherosclerotic Lesions, WHO Technical Report Series No. 143, sets forth methods for grading and classifying atherosclerotic lesions. Methods are recommended for the macroscopic grading of such lesions and for the histological grading of single atherosclerotic plaques. (H.M. Stationery Office, price 1*s*. 9*d*.)

Current Medical Research is a reprint of the articles published in the annual report of the Medical Research Council. They cover a wide variety of subjects and provide concise yet authoritative reviews of current research in subjects such as experimental leukæmia, the mechanism of fever, the genetics of eye disease, and the development of respirators. (H.M. Stationery Office, price 3*s*. 6*d*.)

Expert Committee on Poliomyelitis. Second Report, WHO Technical Report Series No. 145, is a useful compilation of the available data on poliomyelitis inoculation. (H.M. Stationery Office, price 3*s*. 6*d*.)

Young Children in Hospital, by James Robertson. —The developments of the last decade regarding the possible adverse effects on young children of hospitalization (with separation from mother) are reflected in this little book. The author has done much with his films and his investigations to mould opinion on how these effects may be prevented. The book is based upon evidence submitted to the Platt Committee now considering the subject of the welfare of children in hospital and it is valuable to have it available for general reading. Some hospitals have already moved far towards unrestricted visiting of children but there are other matters concerned with hospital procedures discussed by Mr. Robertson in this book. He hints wisely that 'tender loving care' may be wrongly applied. (Tavistock Publications Ltd., price 4*s*. 6*d*.)

First Aid is the authorized manual of the St. John Ambulance Association of the Order of St. John, the St. Andrews Ambulance Association, and the British Red Cross Society. This is the first time that these organizations have published a joint first-aid manual. The result is all that would be expected in a manual published under such auspices, and it is not surprising to learn that it has already run to four impressions, each of 100,000. This is a book which every practitioner and medical student should possess. (Price 4*s*.)

Smallpox and Vaccination is the sixth in the series of 'conquest' pamphlets issued by the Research Defence Society, and answers in simple language questions which may be asked by the lay public. (11 Chandos Street, W.1, price 6*d*.)

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the year ended 31st December, 1957. Part I deals predominantly with the administrative aspects of the National Health Service. The salient financial feature of the year reviewed is that of the total gross cost of the service, which was £537.8 million, the hospitals accounted for £332.3 million, the general practitioner service for £58.5 million, and the pharmaceutical service for £52.9 million.

The number of principals providing unrestricted general medical services was 19,343, of whom 6,381 were in single-handed practices. Compared with the previous year, the number of principals in partnership increased by 448. The vast majority of partnerships consisted of two doctors, and there were only 55 consisting of six doctors or more. There were 1,331 general practitioners aged 66 or over. The number of assistants was 1,465, compared with 1,546 in 1956, and eight of these were aged 76 or over. The average number of patients per doctor was 2,273. The number of general practitioners who attended refresher courses was 1,731 in England and 32 in Wales. (H.M. Stationery Office, price 12*s*.)

Notes on the Diagnosis of Occupational Disease is the second and revised edition of the pamphlet first published in 1950. It is a useful summary of the subject which should be in the possession of every general practitioner. (H.M. Stationery Office, price 3*s*.)

NOTES FROM THE CONTINENT

GERMANY

Gamma-globulin in disseminated sclerosis.—As a result of their observations in 114 cases of disseminated sclerosis, H. Schinko and H. Tschabitscher report that changes take place in the gamma-globulin content of the cerebrospinal fluid, which suggest the formation of immune globulins in the central nervous system. These cerebrospinal gamma-globulin changes do not run parallel with those in the plasma. In addition, they found that sternal puncture performed at the onset of the illness revealed changes similar to those found in infective conditions. The hypothesis is advanced that these findings are compatible with a process of auto-sensitization. It is also claimed that cortisone and its derivatives are of value in treatment.

Polyvinylpyrrolidone in psychiatry.—Polyvinylpyrrolidone is of value in the treatment of those psychotic conditions accompanied by œdema of the brain, according to N. Wolf. Among the conditions mentioned as responding to such therapy are psychoses following cerebral lesions, and 'symptomatic psychoses'. The recommended dosage is 100 ml. thrice daily. Such therapy is said to be followed by rapid waning of symptoms and the disappearance of the twilight state of delirium-coma.

Octogenarian embolectomy.—In reporting two cases of surgical embolectomy in octogenarians —patients aged 84 and 88 respectively—F. Heinzelmann claims that these are the two oldest patients on record, in whom this operation has been successfully performed. His main purpose in reporting these cases is to draw attention to the possibility of the operation being performed successfully at this age in view of the increasing number of people who are surviving into this age-group.

Valves in renal veins.—The current teaching is that the human renal veins are valveless. According to the recently published centenary edition of 'Gray's Anatomy', for instance, valves 'are absent in the very small veins, i.e. those less than 2 mm. in diameter, also in the venae cavae, hepatic, renal, uterine and ovarian veins'. So far as the renal veins are concerned, this view is contested by A. V. Kügelgen and H. Greinemann who, by the use of the stereomicroscope, claim to have found valves in the large renal vein in around 40% of the cases they have examined. In only a small proportion of their cases were the valves well formed, but on the whole they were better formed in the kidneys of fœtuses and children than in those of adults. From this they deduce that some degenerative process takes place with ageing.

Iatrogenic disease.—In issuing a warning against the indiscriminate use of 'ligament and disc injuries' as a diagnostic label, K. Poeck contends that this diagnosis today plays the same rôle as 'colitis' did in the day of Axel Münthe. He emphasizes the well-known fact that patients with psychogenic complaints value highly a diagnosis that sounds learned and definitive. The position is made worse by the tendency to supplement this slipshod diagnosis by equally unfortunate references to 'wear and tear'. Too often the result is that the patient goes away convinced that he is suffering from an incurable condition and submits claims for compensation or sickness benefit accordingly. The other danger involved is that an inadequate examination is carried out, and conditions such as spondylitis, tabes dorsalis or spinal tumours are missed.

Soviet psychiatry.—Psychotherapy in Soviet Russia is still largely based upon Pavlov's work on conditioned reflexes, according to B. Lustig. He notes that the once much vaunted tissue therapy of Filatov and Bogomoletz serum are scarcely used now. What is described as 'psychosurgery' has been forbidden since 1950. Electroconvulsive therapy is regarded with considerable scepticism, but insulin-shock therapy is still widely used, and also sleep therapy. Alcoholism is a major problem in the U.S.S.R., and here again treatment is based upon the conditioned reflex. Brandy and wine are offered to the patient and he is invited to take his fill. He is then given an injection of 0.25 to 0.5 ml. of 1% apomorphine to induce vomiting. The procedure is repeated anything up to forty times until the reflex—'aversion to, and vomiting due to, alcohol'—is well established.

Religion and blood transfusion.—As in the United Kingdom, the increasing use of blood transfusion has raised the problem of those religious sects who refuse such transfusion on religious grounds. These objections are raised most often by the Christian sect known as Jehovah's Witnesses, but some orthodox Jews and Moslems also subscribe to this view. Both the Mosaic writings and the New Testament are quoted as forbidding the use of blood. In view of the consequences that may follow the withholding of blood transfusion in certain cases,

doctors are urged to demand a written statement from all patients, or their relatives, who refuse to have a blood transfusion when it is indicated on medical grounds.

Hospital statistics.—According to figures just published, in 1956 there were 3,360 hospitals in Western Germany, with a total complement of 537,000 beds. These figures do not include the Saar Territory or Berlin. This means that there were 107 hospital beds per 10,000 inhabitants. In 1957, the expenditure for accident compensation rose by 235.7 million DM, an increase of 40% compared with 1956.

ITALY

A hazard of busulphan therapy.—Details are given by D. Gigante of a case in which apparently the therapeutic use of busulphan (1:4-dimethanesulphonyloxybutane) converted a case of chronic myelogenous leukæmia into one of acute leukæmia which ran a rapidly fatal course. The patient responded well to busulphan given for a period of twenty-five days. Treatment was then stopped, but fifteen days later there was a sudden rise in temperature, accompanied by painful splenomegaly, and also hepatomegaly. The patient's condition deteriorated rapidly, with vomiting and diarrhœa, purpura, hæmatemesis and hæmaturia, and the white-cell count rose to 640,000 per c.mm. Differential blood counts revealed 62% of myeloblasts and hæmocytoblasts. Gross anæmia developed and there was a marked fall in the platelet count. The patient died twenty-seven days after treatment with busulphan had been stopped. Although it is admitted that this is a rare complication of busulphan therapy, it is suggested that the fact that it can occur indicates caution in the use of this drug and that it should not be used if other methods of treatment are available.

Peri-arterial neurectomy for cirrhosis of the liver.—L. Vallega and his colleagues have given a detailed account of a patient with cirrhosis of the liver (without ascites) and duodenal ulcer on whom a laparotomy was performed with a view to dealing with the duodenal ulcer. In the end, however, they performed a peri-arterial neurectomy on the hepatic artery below the origin of the gastro-duodenal artery, in order to determine whether this might not improve liver function. The operation apparently was entirely successful from this point of view. Ten months later the patient was in good health and back at work. The liver was only two finger-breadths below the costal margin, its surface was much more regular and it was not painful. There was no splenomegaly or ascites. Liver function tests were all satisfactory, and the albumin/globulin ratio, which preoperatively had been reversed, had returned to normal.

Yttrium^{90}-hypophysectomy.—At a meeting of the Piedmontese Surgical Society, A. M. Dogliotti and A. Ruffo discussed the results obtained with the use of yttrium^{90} as a means of performing hypophysectomy in patients with advanced carcinoma of the breast. The method has several advantages over surgical hypophysectomy: it is easier to carry out, there is practically no operative mortality, and it can be used in patients who are gravely ill. The results to date have been extremely satisfactory in spite of the fact that hitherto the tendency has been to use the method only in advanced cases. It is suggested that if the procedure is limited to those cases in which it has proved useful (carcinoma of the breast, adenoma of the hypophysis, and malignant exophthalmos), and if treatment is initiated at an earlier stage than has hitherto been the case, even better results might be obtained in the future.

Pemphigus as a complication of radiotherapy.—G. Carli reports what he describes as an unusual complication of radiotherapy. The patient was a lady of 64 who received radiotherapy for a tumour of the left upper eyelid. About a year later she developed a bullous pemphigoid eruption which involved the mucous membrane of the mouth as well as the skin. The resulting ulceration of the mouth was so severe as to cause considerable difficulty in swallowing, with a resulting deterioration in the patient's general condition. Treatment with corticotrophin, cortisone, ascorbic acid, and intravenous sulphone had little effect upon the condition.

Cerebellar lesions in poliomyelitis.—Further evidence of the widespread distribution of the lesions that can occur in poliomyelitis is adduced by G. C. Angela and D. Galli in describing the post-mortem changes in two fatal cases of poliomyelitis, in which they found lesions in the cerebellum. The Purkinje cells showed marked chromatolysis, karyorrhexis and poor staining of the nuclei. In varying degrees of severity these changes were found throughout the whole cerebellum. In one case they found small hæmorrhagic foci in the left dentate nucleus.

'Notes from the Continent' are produced in collaboration with the Editors of Bruxelles-Médical (*Belgium*), La Revue du Praticien (*France*), Münchener Medizinische Wochenschrift (*Germany*), and Minerva Medica (*Italy*).

THE PRACTITIONER

Fifty Years Ago

'Many a doubtful and troubled mind haunts this week the lecture-room and the theatre. The neophyte who stands on the threshold of medical science cannot but be abashed, and not a little discouraged, by the vastness of the new field of labour which lies before him'.—*The Lancet*, October 9, 1858, **ii**, 383.

OCTOBER, 1908

'ONCE more', 'Notes by the Way' start, 'we have reached the month in which the medical year begins, and in which freshmen commence, and their seniors resume, their studies at the medical schools. It is a moment which, in the older universities devoted mainly to the "arts",

Carl Harko von Noorden (1858-1944).

arrives, and is allowed to pass, without special recognition by any striking form or ceremony. Nobody is called upon for a speech; everybody drops, more or less quietly, into his place. Nor is there any particular reason why it should be otherwise; for the interests alike of undergraduates and professors are diverse, and the feeling of "*esprit de corps*", which unites them, is by no means due to any habit of labouring together for the advancement of some branch of learning esteemed equally important by all of them. It is only a minority among them, who will continue, or make any practical use of, their studies, after graduation. . . . On the other hand, the contrasting tradition and practice of the medical schools and hospitals is a natural and appropriate reflection of a different order of things. The studies there pursued stand in direct and obvious relation to life. The student there who does not study has no *raison d'être*, and indifference to the results of the researches of the teachers is practically an unknown thing. Whereas there are many Oxford and Cambridge undergraduates, whom the discovery of a lost book by Aristotle or Tacitus would leave cold it is impossible for medical students to adopt that callous tone towards x-rays and anti-toxins. . . . Hence the importance of the annual addresses with which the Medical Sessions are inaugurated'.

Reviewing the comparative mortality of persons engaged in various occupations in England and Wales in the years 1900, 1901, and 1902, the Editor writes: 'So far as the professions are concerned, the death-rate appears to be lightest among clergymen and heaviest among doctors; and the reasons for the difference will be obvious to every medical man. The parson has no night-bell, and is not apt to be rung up for a baptism, as the practitioner is apt to be rung up for an accouchement; nor has he any fear that his income will suffer if he coddles himself when he is unwell instead of paying parochial calls. Indeed, even the well-known clerical liability to laryngitis ought to be diminishing in an age in which ten minutes is considered amply long enough for a sermon; and there are no other ailments specially favoured by the circumstances of the sacred calling. Law, in point of mortality, occupies a position midway between physic and divinity. . . . Publicans . . . die with a frequency which must be surprising even to themselves'.

The opening article, 'On the Pre-operative Treatment of Non-malignant Gastric Disease', is by Arthur E. Barker, F.R.C.S., Professor of Surgery at University College Hospital Medical School. Edred M. Corner, F.R.C.S., Surgeon to the Children's Hospital, Great Ormond Street, writes on 'Fracture and Refracture of the Patella, with some Points in the Treatment'. H. Tyrrell Gray, M.C., F.R.C.S., R.M.O. at Great Ormond Street, contributes 'A Note on the Necessity for End-to-End Apposition in Fractures of Long Bones'.

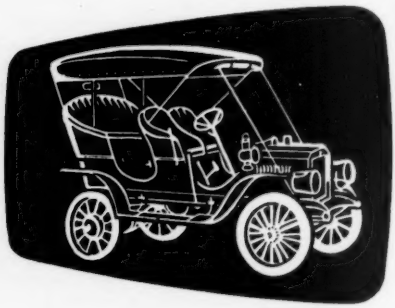
In his 'Review on Venereal Diseases', J. Ernest Lane, F.R.C.S., Surgeon to St. Mary's Hospital and Senior Surgeon, London Lock Hospital, states: 'Notwithstanding the good results, which have been obtained by Metchnikoff, in the prophylaxis of syphilis by the application of strong mercurial ointments, the method is not one upon which absolute reliance can be placed. . . . Measures have recently been adopted in the French Army, which would lead the soldier to believe in the absolute safety of the method, and which would give him a fallacious idea, abolishing in his mind the fear of disease which was one of the best safeguards against its spread, and he would consequently not hesitate to run risks which he would otherwise not have incurred'.

Wilfred Harris, M.D., F.R.C.P., Physician to the Department for Nervous Diseases, St. Mary's Hospital, reviews 'Recent Neurological Literature'. Duncan Matheson Mackay, M.D., Hon. Aurist, Hull, East Yorkshire, and Lincolnshire Institution for the Deaf and Dumb, takes for his subject 'The General Practitioner and Deaf Mutism': 'Sorrowfully, one must admit, deaf mutism is most frequently incurable. There is only one method, by which it can be treated with any reasonable hope of success, and that is —as an Irishman might say—by treating it before it is there to treat. Which saying is but another way of asserting that, while deaf mutism is, as a rule, incurable, it is, not seldom, preventable'.

Twenty books are reviewed this month. The English edition of the third volume of 'Metabolism and Practical Medicine' by Carl von Noorden is described as 'indispensable as a work of reference'. The reviewer notes that 'its appearance is almost simultaneous with the German edition. This is a precedent which we hope will be followed by other translators whenever possible. There is an up-to-date feeling about the work, which would be impossible, if the translation had been deferred until the German edition had been published'. Carl Harko von Noorden, who was born a century ago on September 13, 1858, devoted his whole life to the study of metabolism, particularly in the field of diabetes. He graduated M.D. at Leipzig in 1881, succeeded Nothnagel as professor of medicine at Vienna in 1906, and died on October 26, 1944, in an air-raid. He introduced the oatmeal diet for diabetics and predicted the existence of insulin.

'Confessio Medici' by the writer of 'The Young People' (Stephen Paget) is 'witty, racy and eminently suggestive, and indeed so attractively written that one is loth to put it down unfinished'. There is also a review of the first volume of 'Proceedings of the Royal Society of Medicine'.

W. R. B.



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